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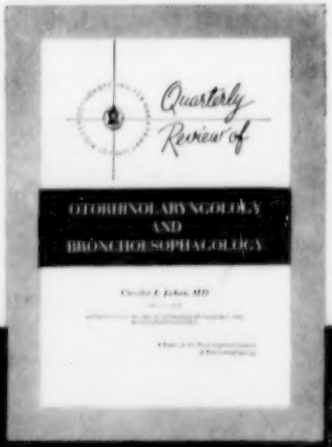

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RECORD OF MEDICINE

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Stress and Disease*

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Two monographs[1, 2] and a series of "Annual Reports"[3–6] have been devoted to a detailed discussion of the literature on stress, a large section of which deals with such conditions as rheumatic diseases, hypertension, renal diseases, arteriosclerosis, etc., which clearly fall within the scope of the INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS. Those who seek detailed information concerning specific clinical aspects of the stress-problem will find a key to the world literature in these specialized publications. It was felt, therefore, that here it would be best to limit ourselves to a brief synopsis of the stress-concept as it presents itself in 1955.

PRECURSORS OF THE STRESS CONCEPT

Ever since man has used the word "disease" he has had some, at least subconscious, inkling of the stress concept. The very fact that a single term can be used to denote a great variety of individual maladies clearly indicates that they have something in common. They possess, as we say, some nonspecific features which permit us to distinguish disease from the condition of health. Yet, because these manifestations are not characteristic of any one disease, they have received little attention in comparison with the specific ones. They were considered of lesser interest for, unlike the latter, they did not help to recognize the "eliciting pathogen" or lend themselves to any effective type of specific therapy.

Nevertheless, several early investigators have attempted to elucidate the mechanisms involved in such nonspecific reactions. Since our knowledge of the nervous system antedates the development of modern Endocrinology, it is understandable that among the two great integrating systems of the body, the nervous and the

* Based on the introductory chapter of the *Fourth Annual Report on Stress*.[6]

The major part of the investigations upon which this article is based was subsidized in part by a Consolidated Grant from the National Research Council of Canada, and in part by the Medical Research Board, Office of the Surgeon General, Department of the Army, Contract No. DA-49-007-Md-186.

hormonal systems, the former was the first to be examined from this point of view. Ricker, Speransky, Reilly, Hoff, and many others have gathered important data concerning the role of the nervous system in such nonspecific reactions as fever, polymorphonuclear leucocytosis, inflammation, etc. In the domain of what may be called "physiologic stress," W. Cannon's studies helped us understand the part played by the sympathetic nervous system and its humoral effector substances.

Furthermore, quite independently, a great deal of progress has been made in the study of pituitary and adrenocortical hormones by chemists, physiologists, and clinicians, too numerous to mention by name.

All the knowledge acquired as a result of these early investigations was indispensable for the eventual formulation of the stress concept, whose leading motive is one of unification. Additional experiments had to be performed, however, to show that the many nonspecific responses of individual target organs are closely integrated and actually represent part of a single biologic response, the general adaptation syndrome. These investigations, which will be outlined below, made it evident that the "stress pattern" of reaction plays an integral part in the most varied physiologic, pathologic, and pharmacologic phenomena.

THE CONCEPT OF STRESS

By a series of experiments on animals it was demonstrated in 1936, that the organism responds in a stereotypical manner to a variety of widely different factors, such as: infections, intoxications, trauma, nervous strain, heat, cold, muscular fatigue or X-irradiation. The specific actions of all these agents are quite different. Their only common feature is that they place the body in a state of general (systemic) stress. Hence, we concluded that the stereotypical response, which is superimposed upon all specific effects, represents the somatic manifestations of nonspecific "stress" itself.

But what is *nonspecific "stress?"* The term had long been used in physics to denote

GLOSSARY OF TECHNICAL TERMS AND ABBREVIATIONS

Stress—a non-specific deviation from the normal resting state, it is caused by function or damage and stimulates repair.

Nonspecific change—a change which can be produced by many or all agents.

Specific change—a change which can be produced only by one or few agents.

G-C—Glucocorticoid (e.g., cortisone, cortisol).

M-C—Mineralocorticoid (e.g., desoxycorticosterone, aldosterone).

A-C—Antiphlogistic corticoid (e.g., cortisone, cortisol). It is essentially synonymous with G-C, since the antiphlogistic, glucocorticoid, lympholytic, and catabolic activity tends to run parallel in the steroids so far examined.

PC—Prophlogistic corticoid (e.g., desoxycorticosterone, desoxocortisone). It is essentially synonymous with M-C, since the prophlogistic activity tends to run parallel with mineralocorticoid activity in the compounds so far examined.

DCA—Desoxycorticosterone acetate or DOCA.

Cortisol—Hydrocortisone, Kendall's compound "F."

STH—Somatotrophic hormone or growth hormone of the hypophysis.

MAD—17-methylΔ^5-androstene-3β, 17β-diol. (Ordinary methylandrostenediol.)

the interaction between a force and the resistance opposed to it. For instance, pressure and tension can put inanimate matter under stress. The above mentioned nonspecific response was thought to represent the biologic equivalent of such physical stress. The term has now been quite generally accepted in this sense not only in English, but—since attempts to translate "stress" led to much confusion—also in most other languages.

THE CONCEPT OF THE GENERAL ADAPTATION SYNDROME

The most outstanding manifestations of this stress-response were *adrenocortical enlargement* with histologic signs of hyperactivity, *thymico-lymphatic involution* with certain concomitant changes in the blood count (eosinopenia, lymphopenia, polynucleosis), and *gastrointestinal ulcers*, often accompanied by other manifestations of *damage or "shock."*

We were impressed by the fact that, while during this reaction all the organs of the body show involutional or degenerative changes, the adrenal cortex actually seems to flourish on stress. We suspected this adrenal response to play a useful part in the systemic, nonspecific adaptive reaction, which we visualized as a "call to arms" of the body's defense forces, and called it the "alarm reaction."[7]

Subsequent studies showed that the alarm reaction is but the first stage of a much more prolonged *General Adaptation Syndrome*. The latter comprises three distinct stages, namely:

(1) *the alarm reaction* (A-R), in which adaptation has not yet been acquired.
(2) *the stage of resistance* (S-R), in which adaptation is optimal.
(3) *the stage of exhaustion* (S-E), in which the acquired adaptation is lost again.

THE MECHANISM OF THE GENERAL ADAPTATION SYNDROME

In order to elucidate the kinetics of this syndrome we proceeded as follows:

Rats were *adrenalectomized* and then exposed to stressor agents. This showed that in the absence of the adrenals stress can no longer cause thymico-lymphatic involution or characteristic blood count changes.[8] When adrenalectomized rats were treated with the impure cortical extracts available at that time, it became evident that thymico-lymphatic involution and the typical blood count changes could be produced by adrenal hormones even in the absence of the adrenals. Therefore, these changes were considered to be indirect results of stress mediated by corticoids.[8, 9]

Conversely, the gastrointestinal ulcers and other manifestations of pure damage or shock were actually more severe in adrenalectomized than in intact animals and could be lessened by treatment with cortical extracts. It was concluded that these lesions are not mediated through the adrenal; in fact, they are actually combated by an adequate adrenocortical response to stressor agents.[8]

But what stimulates adrenocortical function during stress? In the course of the next year, we found that among many surgical interventions tried, only *hypophysectomy* prevents the adrenal response during the alarm reaction. Hence, we concluded that stress stimulates the cortex through an adrenocorticotrophic hormone, now known as ACTH.[10, 11]

Then pure cortical steroids first became available through the classic investigations of Kendall and Reichstein. With these, we could show that administration of *mineralo-corticoids* or *M-Cs* (such as desoxycorticosterone) produces experimental replicas of the so-called *hypertensive and inflammatory "rheumatic" diseases, notably, nephrosclerosis, hypertension, vascular lesions* (especially periarteritis nodosa and hyalin necrosis of arterioles.)[12] Arthritic changes resembling, in acute experiments, those of rheumatic fever and, after chronic treatment, those of rheumatoid arthritis were also evident.[13] Yet, even very high doses of mineralo-corticoids did not induce any noteworthy thymico-lymphatic or blood count changes, such as those caused by cortical extracts.

Significantly, exposure of animals to certain nonspecific stressor agents (e.g., cold) produced marked adrenocortical enlargement and organ changes very similar to those elicited by the administration of mineralo-corticoids.[14] Still, many investigators doubted that secretion of M-Cs could be involved in the pathogenesis of disease, since the very existence of natural, endogenous M-Cs was questioned. Indeed until quite recently some of the most eminent students of the adrenal advocated the "unitarian theory," which held that the gland secretes only one corticoid, so that a derangement in the balance between antagonistic cortical hormones would be impossible. This concept was definitely disproved by the isolation of *aldosterone* from both the tissue and the venous blood of the adrenals.[15]

Extracts rich in *gluco-corticoids or G-Cs* (such as cortisol and cortisone) on the other hand, were highly potent in causing *thymico-lymphatic* involution and in eliciting characteristic blood count changes of the alarm reaction. They also tended to inhibit the inflammatory "rheumatic-like" changes which can be elicited in animals by mineralo-corticoids. Thus, in many respects, the two types of corticoid hormones antagonize each other.[1, 9]

Another interesting activity of the corticoids, discovered at this time, is their singular effect upon the *central nervous system* of animals. A variety of steroids, among which figured both G-Cs (e.g., cortisone) and M-Cs (e.g., DCA), as well as other steroid hormones and hormone-metabolites (e.g., pregnanediol, pregnanedione), proved capable of causing a state of great excitation and confusion, followed by marked depression of all reflex activities and, eventually, deep anesthesia.[16] This observation raised the question of whether a pronounced increase in the activity of endogenous corticoids could be responsible for certain nervous and emotional accompaniments of exposure to stress. After the introduction of cortisone in clinical therapy, it became evident that this hormone exerts a powerful effect upon the central nervous system in man. In animals, both G-Cs and M-Cs exhibit this effect, making it necessary to watch for the effect as soon as patients are treated with large doses of aldosterone.

The terms "gluco-corticoids" and "mineralo-corticoids" emphasize the salient metabolic actions of these substances. From a clinical viewpoint, however, their effects on inflammation are perhaps of even greater interest. Since the gluco-corticoids inhibit inflammation, while the mineralo-corticoids enhance it, the G-Cs may appropriately be called "*antiphlogistic corticoids*" or "*A-Cs*," and the M-Cs "*prophylogistic corticoids*" or "*P-Cs*," when they are discussed with reference to their effects on inflammation. It remains to be seen, however, whether G-C and A-C (or M-C and P-C) activities necessarily run parallel in all steroid compounds, including those (like aldosterone) which have not yet been fully examined for such effects.

Inflammatory granulomas, especially those produced in the vicinity of joints by the local application of irritants (e.g., formalin, mustard powder), as well as certain allergic reactions, are likewise aggravated by P-Cs and inhibited by A-Cs. Apparently, the response of the adrenal cortex is important not only in the defense against systemic stress (affecting the whole organism), but also in the manifold topical defense reactions which occur upon exposure to *local stress* (e.g., bacterial or chemical irritants, response of a "shock organ" to an allergen).[1, 17] These findings helped to formulate the concept of the Local Adaptation Syndrome (L-A-S) to be discussed below [cf. p. 283].

In this connection, the hormone sensitivity of certain so-called "*anaphylactoid inflammatory reactions*" is of special interest. Actually, attention had first been called to a possible relationship between the adrenal cortex and inflammation by an incidental observation on rats given parenteral injections of egg white. It was found that the rat is naturally hypersensitive to egg white and responds to the intraperitoneal or intravenous administration of this substance by an acute serous inflammation of the paws and snout. This inflammatory response was greatly aggravated in adrenalectomized animals (presumably because they could not defend themselves by the endogenous production of A-Cs). On the other hand, it was prevented by treatment with systemic stressors directly in proportion to the adrenocortical enlargement they produced (presumably, as a result of excess A-C secretion).[11] Subsequently, it could be shown that cortisone and ACTH inhibit, while certain crude anterior-pituitary preparations and desoxycorticosterone aggravate this anaphylactoid type of acute inflammation.[18]

Curiously, our crude anterior-pituitary extracts also duplicated most of the above mentioned actions of P-Cs upon the *cardiovascular system, the blood pressure, the connective tissue (inflammation), and the kidneys*.[9, 19] The hypophyseal preparations which we used were definitely corticotrophic in that they enlarged the adrenal cortex but were also particularly rich in the so-called "growth hormone" or *somatotrophic hormone* (STH). This made it difficult to interpret early experiments in which such crude extracts were used, since we were unable to distinguish clearly between the effects of ACTH and STH. However, as soon as we obtained purified ACTH, it became evident that the above mentioned pathogenic actions of the crude anterior-pituitary preparations could not be due to their ACTH content, since even the highest tolerable doses of the pure corticotrophic hormone failed to duplicate their predominent P-C effects. On the other hand, overdosage with purified STH caused cardiovascular and renal lesions, virtually identical with those previously observed in animals treated with P-Cs. It was then concluded that the characteristic actions of crude anterior-pituitary preparations were due mainly to their STH content. The extent to which STH acts indirectly by stimulating the P-C production of the adrenal cortex, or directly by sensitizing the peripheral tissues to P-Cs remains to be seen. Preliminary observations suggest that the last-mentioned mechanism is the more important although both may be implicated.[20] This point is not yet settled.

From the internist's point of view, perhaps the most interesting feature of STH in the adaptation syndrome is that it can effectively *combat catabolism and susceptibility to infections*. Animals heavily overdosed with ACTH or A-Cs tend to lose a great deal of weight. Eventually they die, frequently as a result of generalized septicemia caused by normally saprophytic microorganisms. In rats, the lung tissue appears to be singularly predisposed to such infections. Under these conditions, adequate doses of STH prevent the loss of body weight as well as excessive microbial

proliferation.[21] The value of these actions of STH in the management of infections in man has yet to be proved, but experiments on rats have already demonstrated the great influence of adaptive hormones on resistance to the human type of tuberculosis. Normally, the rat is virtually resistant to tuberculosis bacilli; it may be rendered sensitive by ACTH or A-Cs and this sensitivity can, in turn, be abolished by STH.[22, 23]

CONDITIONING OF HORMONE ACTIONS

As work along these lines progressed, it became increasingly obvious that the activity of the hormones produced during stress depends largely upon a variety of "conditioning factors." Both the production of the "adaptive hormones" and their effect on individual target organs proved to be greatly influenced by heredity, age, previous exposure to stress, the nutritional state, etc. For instance, the production of corticotrophic hormone by the pituitary is enhanced by a high protein diet, while the action of M-Cs upon most target organs is augmented by excess sodium.[9]

Stress itself is perhaps the most effective and most common factor capable of conditioning the actions of adaptive hormones. Thus systemic stress augments the antiphlogistic, lympholytic, catabolic, and hyperglycemic actions of A-Cs, while the salient effect of the adaptive hormones, that of modifying the course of inflammation, naturally cannot manifest itself unless some topical stressor first elicited a phlogistic response.

Ingle[24] introduced the concept of the "permissive actions" of corticoids. This term implies that the adrenal hormone does not affect a target of stress itself, but permits a stressor to act upon it. Furthermore, the alleged presence or absence of a permissive factor can only allow or disallow a reaction, but is unable to vary its intensity. To illustrate this concept one might compare the production of light by an electric lamp to the biologic reaction, and the switch to the "permissive factor." The switch cannot produce light, nor regulate the degree of its intensity, but unless it is turned on the lamp will not function. Correspondingly, the functional signs, generally considered to be characteristic of corticoid-overproduction during stress, would not result from any actual increase in corticoid secretion but from the extra-adrenal actions of the stressors themselves. The presence of corticoids would be necessary only in a "supporting capacity" to maintain the vitality and reactivity of tissues.

Actually, it is precisely in the specific and not in the nonspecific stress reactions that the corticoids play a purely "permissive role" of this type. Here they are necessary only to prevent stress and collapse thus keeping the tissues responsive. For instance, adrenalectomized rats will not respond to injected STH with somatic growth, or to sexual stimulation with mating without a minimal maintenance corticoid treatment. These reactions are in fact not characteristic of the corticoids and could not be duplicated in the absence of the specific stimulus, even with the highest doses of corticoids. The characteristic functional signs of A-C overproduction which we see in the alarm reaction (e.g., atrophy of the lymphatic organs, catabolism, inhibition of inflammation) are also impeded by adrenalectomy and restored even by mere maintenance doses of A-Cs in the presence of stress, which sensitizes or "conditions" the tissues to them. However, unlike specific actions, these nonspecific effects can also be duplicated in the absence of any stressor if large doses of A-Cs are given. (Cf. *Fourth Annual Report on Stress*, pp. 78–85.)

The importance of such conditioning influences is particularly striking in the regulation of stress reactions, since in the final analysis they are the factors which can actually determine whether exposure to a stressor will be met by a physiologic adaptation syndrome or cause "diseases of adaptation." Furthermore, in the latter instance, these conditioning factors can even determine the selective breakdown of one or the other organ. We are led to believe that differences in predisposition, due to such factors, might explain why the same kind of stressor can cause diverse types of "diseases of adaptation" in different individuals.

It was only on the basis of such experiments that the mechanism through which stress affects the adrenal cortex could be clarified. We noted that stressors such as "formaldehyde, which caused marked adrenal hypertrophy in the normal but not in the hypophysectomized animal, remained without effect (upon the adrenal) if the adrenal cortex was prevented from undergoing atrophy by the administration of pituitary extract. The effect of such a drug on the adrenal appears to be an indirect one due to pituitary stimulation."[10]

THE CONCEPT OF THE LOCAL ADAPTATION SYNDROME

It had long been known that many local responses to injury are nonspecific. It had been noted, for instance, that a variety of "topical stressors" (burns, microbes, drugs) share the power of producing nonspecific tissue damage and/or inflammation. However, it is only recently that the close relationship between systemic and local types of nonspecific reactions has been more clearly established. While the characteristic response of the body to systemic stress is the general adaptation syndrome, characterized by manifold morphologic and functional changes throughout the organism, topical stress elicits a local adaptation syndrome whose principal repercussions are confined to the immediate vicinity of the eliciting injury. They consist on the one hand of degeneration, atrophy, and necrosis, and on the other of inflammation, hypertrophy, hyperplasia, and, under certain conditions, neoplasia.

LOCAL ADAPTATION SYNDROME AND GENERAL ADAPTATION SYNDROME

At first sight, there appears to be no striking similarity between the systemic and the local reaction-type. A patient in traumatic shock furnishes a characteristic example of the general adaptation syndrome and, in particular of its earliest stage, the "shock phase" of the general alarm reaction. An abscess, formed around a splinter of wood represents a typical example of the local adaptation syndrome, and in particular of its "stage of resistance," during which the defensive inflammatory phenomena predominate. On the surface these two instances of disease reveal no striking similarities and yet careful study shows them to be closely related.

The experimental observations which led us to these conclusions have been described elsewhere.[25, 26] The general adaptation syndrome and the local adaptation syndrome are thought to be interrelated because:

1. Both are nonspecific reactions, comprising damage and defense.
2. Both are triphasic with typical signs of "crossed resistance" or, depending upon the stressors used, "crossed sensitization" during the second stage.
3. Both are singularly sensitive to the so-called "adaptive hormones" (ACTH, STH, corticoids).
4. If the two reactions develop simultaneously in the same individual, they greatly influence one another. That is systemic stress markedly alters tissue reactivity to local stress and vice versa.

THE CONCEPT OF THE DISEASES OF ADAPTATION

Thus we arrived at the conclusion that the pathogenicity of many systemic and local stressor agents depends largely upon the function of the hypophysis-adrenocortical system. The latter may either enhance or inhibit the body's defense reactions against stressors. We think that derailments of this adaptive mechanism are the principal factors in the production of certain maladies considered to be essentially diseases of adaptation.

It must be kept in mind that such diseases of adaptation do not necessarily become manifest during exposure to stress. This is clearly demonstrated by the observation that temporary overdosage with desoxycorticosterone can initiate a self-sustaining hypertension, which eventually leads to death long after hormone administration has been discontinued. Here, we speak of "meta-corticoid" lesions. The possibility that a temporary excess of endogenous aldosterone could induce similar delayed maladies deserves serious consideration.

Among the derailments of the general adaptation syndrome which may cause disease, the following are particularly important:

1. ***An absolute excess or deficiency*** in the amount of adaptive hormones (e.g., corticoids, ACTH, STH) ***produced*** during stress.

2. An absolute excess or deficiency in the amount of adaptive hormones ***retained or fixed*** by the peripheral target organs during stress.

3. A ***disproportion*** in the relative secretion (or fixation) during stress of various antagonistic adaptive hormones (e.g., of ACTH and A-Cs, on the one hand, and of STH and P-Cs, on the other).

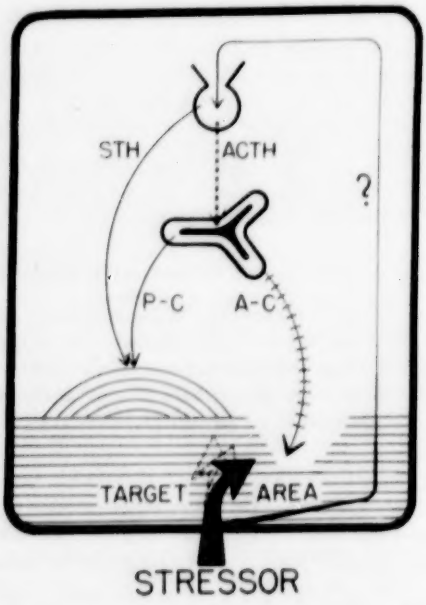
4. Production by stress of metabolic derangements, which abnormally alter the ***target organ's response*** to adaptive hormones (through the phenomenon of "conditioning").

5. Although the hypophysis-adrenal mechanism plays a prominent role in the general adaptation syndrome, ***other organs*** which participate in the latter (e.g., nervous system, liver, kidney) may also respond abnormally and become the cause of disease during adaptation to stress.

SUMMARY OF OBSERVATIONS

To summarize we might say that all agents which act upon the body or any of its parts exert dual effects:

1. *Specific actions*, insofar as they modify the nonspecific actions of the same agents.



2. *Nonspecific or stressor effects*, whose principal pathways, so far as we know them today, are illustrated in figure.

The *stressor acts* upon the target (the body or some part of it) directly (thick arrow) and indirectly through the pituitary and adrenal.

Through some *unknown pathway* (labeled by a question mark), the "first mediator" travels from the directly injured target area to the *anterior pituitary*. It notifies the latter that a condition of stress exists and thus induces it to discharge ACTH.

It is quite possible that this "first mediator" of hormonal defense is not always the same. In some instances it may be an adrenaline discharge, in others a liberation of histamine-like toxic tissue metabolites, a nervous impulse or even a sudden deficiency in some vitally important body constituent (such as glucose or an enzyme).

ACTH stimulates the *adrenal cortex* to discharge corticoids. Some of these, the *prophlogistic corticoids* (P-C), stimulate the proliferative ability and reactivity of connective tissue; they enhance the "inflammatory potential." Thus, they help to put up a strong barricade of connective tissue through which the body is protected against further invasion by the pathogenic stressor agent.

However, under ordinary conditions, ACTH stimulates the adrenal more effectively to secrete *antiphlogistic corticoids* (A-C). These inhibit the body's ability to put up granulomatous barricades in the path of the invader. In fact, they tend to cause involution of connective tissue with a pronounced depression of the inflammatory potential. Thus they open the way to the spreading of infection.

It is not yet known whether ACTH always stimulates the adrenal to produce the various corticoids in the same proportions and with a predominance of A-Cs. Certain recent experiments[37] suggest that, depending upon conditions, ACTH may cause the predominant secretion of one or the other of the steroid hormones. However, the *somatotrophic hormone* (STH) of the pituitary increases the inflammatory potential of connective tissue, very much as the P-Cs do. Hence, it can sensitize the target area to the actions of the latter.

It is possible that the hypophysis also secretes a special corticotrophin which induces the adrenal to elaborate predominantly P-Cs. Indeed, STH itself may possess such effects, but this has not yet been proved. In any event even if ACTH were the only corticotrophin, the actions of the corticoids produced under its influence could be vastly different depending upon "conditioning factors" (such as STH) which specifically sensitize the target area for one or the other type of corticoid action. Actually, conditioning factors could even alter the response to ACTH of the adrenal cortex itself, so that its cells would produce more A-Cs or P-Cs. Thus, during stress, one or the other type of effect could predominate.

The fundamental reaction pattern to topical stressors is a local adaptation syndrome with inflammation, to systemic stressors the general adaptation syndrome. Various modifications of these two basic responses constitute the essence of most diseases.

OUTLOOK SUGGESTED BY THESE OBSERVATIONS

Pasteur, Koch, and their contemporaries introduced the concept of specificity into medicine, a concept which proved to be of the greatest heuristic value up to the present time. Each individual, well-defined disease, they held, has its own specific cause. It has been claimed by many that Pasteur failed to recognize the importance of the "terrain," being too preoccupied with the pathogen (microorganism) itself. His work on induced immunity shows that this is incorrect. Indeed, at the end of his life he is reported to have said: "Le germe n'est rien; c'est le terrain qui est tout."

The theory which directed the most fruitful investigations of Pasteur and his followers was that the organism can develop specific adaptive reactions against individual pathogens and that by imitating and complementing these, whenever they are short of optimal, we can treat many of the diseases which are due to specific pathogens.

To our mind the general adaptation syndrome represents, in a sense, the negative counterpart or mirror image of this concept. It holds that many diseases have no

single cause, no specific pathogen, but are largely due to nonspecific stress and to pathogenic situations which result from inappropriate responses to such nonspecific stress.

The blueprint of the pathways through which stress acts may be partly incorrect; it is certainly quite incomplete. But in it we have a basis for the objective scientific dissection of such time-honored, but hitherto rather vague concepts as the role of "reactivity," "constitution and resistance" or "nonspecific therapy," in the genesis and treatment of disease.

If we may venture a prediction, we would reiterate the opinion *that research on stress will be most fruitful if it is guided by the theory that we must learn to imitate, and if necessary to correct and complement, the body's own autopharmacologic efforts to combat the stress factor in disease.*

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A Footnote to Medical History

CONCERNING THE ARTICLE BY HANS SELYE ON "STRESS AND DISEASE"

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DISEASE AND HISTORY

One of the most important and least known facets of disease, philosophically considered as a nosological entity, is the role it plays in heralding historic situations.

Because of its impact on man as a living being and on society as a community of men, disease can change the face of History. Malaria contributed to the disintegration of the Roman Empire, and the bubonic plague dug the grave in which the Middle Ages were buried. Sometimes, however, instead of changing a historic situation, disease announces its coming. Syphilis, then a "new "disease, announced the imminent arrival of the Renaissance, while psychoneurosis, raised almost to a poetic level by Freud, was a sort of medical prelude to our century. Stress, a concept first formulated by Hans Selye in 1936, is perhaps the most typical exponent not only of new directions in Medicine, but of the gravest social and psychological problem of our civilization.

Human beings can no more invent disease than disease alone can create History, even though it may change it. Very often diseases incarnate historical crises. The medieval plague marked a crisis in public health or hygiene, which had been raised to a high level by the Greeks and Romans but had decayed with the advent of Christian philosophy. Syphilis foreshadowed the Renaissance crisis, a crisis motivated by other factors—the discovery of gunpowder, the crossing of the Atlantic, the end of feudalism, the return to classical philosophies—but translated into a "new" disease which would obsess man until Ehrlich's day. Neuroses, as Freud explained them to a timorous society embarrassed by an excess of taboos, revealed the crisis that existed between the individual's innermost life governed by the pleasure principle and his outer life governed by the moral conventions of society.

When Selye formulated his stress theory, he was crystallizing a new historical current and anticipating the newest tendencies in Medicine which were just then being adumbrated.

THE "DEFENSIVE" STAGE OF ENDOCRINOLOGY

Modern Endocrinology is scarcely sixty years old, if we establish its birth on the day G. B. Murray treated a cretin with a thyroid extract. For the first ten years the new science was inspired by the concept that the endocrine glands possessed a predominantly *antitoxic* function and that their secretions neutralized circulating blood poisons.

The next ten years saw progress in our knowledge of the *metabolic* function of the endocrine glands, an idea which still prevails in Medicine today, for we have proved

that the endocrine glands govern the finest and most subtle enzymatic processes on which the functioning of the entire organism depends.

Less than twenty years ago Selye formulated the idea of the *defensive* function of the endocrine glands. That function was not defensive in any specific sense against given poisons, as was the belief in the aforementioned antitoxic stage, but rather *defensive* in a generic way against all infections, intoxications, tensions, shock, excesses of all kinds, and stress, which the human being may suffer in both body and mind.

The stress theory propounded by Selye, who in spite of being essentially a research man has always had a subtle clinical insight, is a revolutionary reaction against the etiologic tyranny of specificity, which dictated over Medicine ever since the beginning of the great bacteriologic discoveries at the end of the last century. Contrary to the etiologic concepts which, from Pasteur's time on, directed the course of diagnostic and therapeutic studies in Medicine, Selye's work, with clear perspective, has restored the importance of the terrain as against the germ, of the body as against its toxic or microbial aggressors. Thus the current "new" ideas of organic functional unity and psychosomatic medicine have been harmoniously integrated into the concept of stress which so typically represents the historicultural spirit of Medicine in our times.

THREE BASIC PRINCIPLES OF THE STRESS CONCEPT

Hans Selye's article, published in this issue of the INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS, ratifies the growing conviction that the concept of stress has introduced into modern Medicine several principles of enormous practical value:

First, that in response to the most heterogeneous and least specific aggressions the *whole* organism is involved, especially the neuroendocrine, humoral, and enzymic systems of functional correlation. This concept has been important in pointing out new directions for the treatment of the *entire* patient, integrating, for example, antibiotics with vitamins in the treatment of infections, thus combining in one single medication maximum specificity therapies with therapies that represent the acme of therapeutic unspecificity.

Second, that the general adaptation syndrome reveals more and more in the clinic how disproportionate the organic reaction is with regard to a stimulus or aggression. The organism reacts to nonspecific—or specific—aggressions in an exaggerated, incommensurate way with an excess of circulating corticoid hormones and vascular reactions, excesses which may lead a patient of "slight endocrine reserve" to adrenocortico exhaustion. The alarm signal of the pituitary-adrenal axis (why doesn't Selye add the thyroid to his "stress axis"?) excites an emergency—and excessive—response of the organism to the danger which threatens it at the moment of stress.

And finally, that in all organic reactions—specific and nonspecific—to aggression, the organism responds in such a way as to denote a return to a *less differentiated biologic phase*. Our physiology and psychology are organized to respond to "normal" situations, but in an emergency, the civilized physiopsychological rigging collapses and we return—even biologically—to a "prehistorical" epoch of undifferentiation:

in other words, when there is danger, the glands, the organs, the different organic systems, return to a phase of indifferentiation, or at least of less differentiation. The organism responds in this way with an excessive generosity of inflammatory (in the *local* reaction to stress), humoral, and psychic reactions to a stress situation which threatens the organofunctional unity of the organism.

The human being possesses several "defense planes," the most superficial being Cannon's classical sympathicoadrenal "emergency system," and the deepest Selye's diencephalic-pituitary-adrenal axis. On these "planes," a delicate chain of endocrine correlations enables the organism to defend itself against the stress which threatens the constancy of the "inner milieu," described by Claude Bernard, and the continuity of human life. Paradoxically, although the human being can live without his "system of acute alarm" and yet face emergency situations, he cannot survive without his "system of chronic alarm" that responds to that "chronic situation of alarm" which is human life itself.

STRESS AND MODERN MEDICINE

Selye did not usher in what some call the "Adrenal Age" of Medicine, but when he focused universal attention on stress as the biopathological crossroads of modern Medicine, he contributed to the harmonious integration of Psychiatry and Neurology, Endocrinology, and Nutrition, the normal and the abnormal, in a syndrome which is of enormous importance not only clinically as a research tool, but from the historicocultural point of view.

It is understandable, then, that stress has become one of the main fields of study in modern Medicine in our Atomic Age, which with its tremendous international tensions, its constant threats of nuclear holocausts, and its apocalyptic visions of a future of destruction, has replaced the peaceful "Aspirin Age," as Ortega y Gasset called the last century when people who forsook active happiness were content to assuage their small griefs with mild melancholy drugs bearing musical names.

A historic situation frequently crystallizes into a discovery. This is what happened with chloroform which ushered in the era of anesthesia, carbolic acid which ushered in the antiseptic era, the smallpox vaccine which initiated modern immunology, and penicillin which started the antibiotic era. The response is to a pressing medical need, and clinical interest in a problem which suddenly becomes very important to society announces the fact that such a problem contains one of the keys to the philosophical currents prevalent at that particular moment of history.

Universal interest centered today upon the concept of stress is the harbinger of what the next objective of Medicine will be: concentration on disease coming from *within* (psychosis, metabolic, and degenerative diseases) as progress is made in eradicating diseases coming from *without* (infections, shock, and exogenous intoxications). The human being today is preoccupied with stress because stress is the biopsychopathological subsoil of his organism, as well as of society and of the present historical moment.

We might use von Weizsaecker's classification and say that, as we have overcome *biosis* or the reversible modifications of cellular structures caused by infections, toxins or shock which are manifested in the entire human body, there has been an increase

of *neuroses* or diseases caused by pure functional alteration of the rhythm and proportion of the biologic phenomena of absorption, secretion, and chemism, and of *scleroses* or irreversible structural modifications located in only one part of the body. From the chronological point of view, *scleroses* represent what is historicobiographical and permanent in disease as against what is temporary in *biosis*, and as against what is achronological, not situated in time, in *neuroses*. The stress theory is a common denominator for the three aforementioned disease categories of Weizsaecker.

STRESS AND THERAPY

The stress concept is revised and brought up to date every year, thanks to the zeal and application of its originator. Hans Selye does not allow his theory to petrify in time and to become—as has happened with so many other theories—a fossil of thought; he keeps it alive, growing, changing like a living being, reappearing with new colors and additions every season.

"Death goes wherever the body goes," says an old Spanish proverb. Stress goes everywhere hand in hand with the healthy or diseased human body, and represents as important a perspective to the clinician, who is interested in the human body and tries to ascertain the reason for its reactions so that he may complete and correct them, as to the medical philosopher, who is interested in diseases as exponents of the historicocultural climate of each period.

The stress theory represents furthermore a sober therapeutic lesson. The body in its "autopharmacological efforts"—to use Selye's expression—is excessively generous in its reactions and may injure itself in its adaptation efforts. The best physician is the one who in his therapy soberly supplements these efforts of the organism and *nothing more*. He who applies to therapeutics the classic advice on what every knight should do with his sword: "Never unsheathe it without reason, and never put it back without honor."

GORDON CONFERENCE ON BLOOD CHEMISTRY

One of the Gordon Research Conferences, sponsored by the American Association for the Advancement of Science, will be held this year on the form, stability, and other biochemical properties of blood and blood lipids. It will take place at the Kimball Union Academy, Meriden, New Hampshire, from June 13–17, 1955.

Reservations and other information may be obtained from Dr. Herbert L. Davis, Wayne County General Hospital, Eloise, Michigan. Accommodation is limited to 100 persons.

Editorial Survey

Capillaries in the Limelight

Capillary vessels, so long taken for granted in physiology, are receiving a growing share of attention in biochemical and medical fields. Disease entities seemingly as disparate as rhinitis and poliomyelitis have recently been linked with capillary dysfunction.

The capillaries, it may be recalled, are vessels ranging in diameter from about 8 to 20 microns which pervade almost every tissue in the body. The smallest are those of the brain and intestinal mucous membrane; the largest are those in the skin and bone marrow.

Any disturbance of the organism's biologic equilibrium may involve the capillaries in the unhappy vicious circle so well described recently by Biskind and Martin.[1] Insufficient local nutrition of tissues, anoxia, or chemical, physical or psychogenic stress can cause increased permeability of capillary vessels. Parenthetically, stress of any kind usually alters the *p*H of body fluids and could upset the normal anion-cation balance at the cell membrane. The more permeable capillaries now allow certain large molecules of infective agents, or the molecules of their by-products, to penetrate the capillary walls. The invading agents further increase capillary permeability, thereby setting off the familiar chain reaction of inflammation, edema, and vascular damage.

Thus the familiar stress syndrome of Selye is joined by what Eppinger[2] first called the "capillary syndrome." A number of workers have since shown that this syndrome is present in a variety of diseases, particularly in those caused by viral infection. For example, in viral hepatitis we first see gross injury to the capillary system of the hepatic lobules followed by a disturbance in blood flow. This in turn causes destruction of cells in the central part of the hepatic lobules and finally results in transudation into tissues and acute hepatic necrosis.

In poliomyelitis, a number of workers have noted that edema resulting from vascular disturbances plays an important part in the destruction of neurons. Boines[3] noted that nearly all 400 patients with acute poliomyelitis were found to have abnormal capillary fragility. The capillary syndrome was also observed in cases of smallpox, measles, primary atypical pneumonia, mumps, and virus A influenza, according to Sokoloff's[4] review of the field. Capillary permeability is also probably responsible for a large part of the vascular engorgement and edema of mucous membrane that accompany the misery of a common cold.

The emergence of a new trend in therapy called the "capillary-flavonoid school" is the result of hundreds of painstaking biochemical experiments. The last 10 years saw the astounding development of antibiotic therapy based on the principle of attacking invading microorganisms with bacteriostatic or bactericidal agents. Yet it is known that during that period many microorganisms learned to throw up defenses, either through resistance or adaptation.

The new "school" would seem to proceed from the basis that most pathogenic agents entering the organism, such as pollen, bacteria, or viruses are, in the final analysis, "foreign molecules." Before these molecules can cause serious damage they must penetrate cellular or tissue membranes. While the body is endowed with natural defenses to shut out these invaders, the new therapy would attempt to strengthen some of the defenses at their weakest points. The most potent weapon at present seems to be the group of substances called citrus bioflavonoids, or vitamin P flavones.

Most of our present knowledge of flavonoids originates from the pioneer work of Szent-Gyorgyi's group in 1936 on hesperidin, a substance found to influence capillary function. Hesperidin is present in citrus fruits and certain vegetables, notably some members of the pepper family. However, a good deal of it is lost in peeling, cooking, and processing. For example, a whole orange, peeled to leave the white substance intact, contains 10 times as much hesperidin as an equal weight of strained orange juice.

Reports of clinical experience with the flavonoids are appearing more and more frequently in the literature. Biskind and Martin[1] reported the rapid subsidence of symptoms in 69 cases of acute respiratory infections, including the common cold, acute follicular tonsillitis, and influenza. Therapy consisted of 200 mg. to 1.6 Gm. of the citrus flavonoid complex (vitamin P complex) combined with ascorbic acid. No ill effects were observed in this series, nor in Sokoloff's treatment of influenza with double the dosage.

In a historical vein, the use of citrus juices in respiratory infections is supported by a long tradition in folklore and "old wives' remedies." It may be recalled that certain African tribes have for generations combated various fevers with a decoction of boiled red peppers, a plant extremely rich in vitamin P flavones.

Returning to the present, the growing interest in the new therapeutic approach is shown by the first "Conference on Bioflavonoids and the Capillary" held in New York in February of this year and organized by the New York Academy of Sciences. Reports at that conference offered some encouragement that the bioflavonoid-ascorbic acid combination may be beneficial in the treatment of rheumatic fever, habitual abortion, and certain blood dyscrasias.

Dr. Szent-Gyorgyi speaking at the conference said: "There is no doubt that our body is dependent on an outside supply for the classical vitamins under any condition. But there may also be vital substances which our body can produce under normal conditions but is unable to synthetize under exceptional circumstances, as stress, infection or the influence of some genetic shortcoming. In such a condition our body would become dependent on an outside supply. . . . a conditioned avitaminosis may also be at the bottom of other degenerative diseases."

On that occasion the speaker had brought with him a small tube containing an intensely yellow substance extracted from the thymus gland of an animal. He stated that more work would be required before the substance could be identified as an endogenously produced flavonoid. This work is being done in an increasing number of laboratories. It is hoped that the "capillary-bioflavonoid" school may open up an entirely new area in man's struggle against environmental invaders.

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Dr. Hans Selye Joins International Editorial Board

The Editors are honored to announce that Dr. Hans Selye has accepted an appointment to the Editorial Board of International Record of Medicine and General Practice Clinics. Doctor Selye is Professor of Histology and Director of the Institute of Experimental Medicine and Surgery at the University of Montreal.

Symposium on Chlorpromazine in Clinical Medicine

We present in this issue a Symposium on the remarkable new drug, chlorpromazine, which has obtained such dramatic success in psychiatric and neurologic practice.

The distinguished clinicians from the United States and Europe review the field in its psychiatric, pharmacologic, neurologic, and other aspects. This field is widening all the time, and the limits of therapeutic usefulness of this new drug have not yet been reached.

Can It Be Said That Chlorpromazine Has Specific Properties?

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Chlorpromazine, despite its recent discovery, has aroused an interest excelled by few pharmaceutic products in the past. Since it was first introduced four years ago in the therapeutic armamentarium, its pharmacologic activity and many clinical uses have been the basis of hundreds of reports. These studies have not exhausted the subject and its mode of action is still a lively topic.

Therefore, we felt it would be interesting to outline briefly the history and development of chlorpromazine and to define its pharmacologic and physiologic properties.

Chlorpromazine (I) is a base with a fairly simple chemical structure derived from phenothiazine (II), the latter product being a heterocyclic compound containing carbon, hydrogen, nitrogen, and sulphur in its molecule.

Phenothiazine was first synthesized by Bernthsen in 1883.[1] Chemically, phenothiazine is closely related to various dyes and especially to methylene blue; however, it was only in 1934 and following the work of Campbell et al[2] that this base was found to possess insecticide properties which made it useful for agriculture. In 1938, Harwood, Jerstad, and Swanson[3] discovered its activity in swine ascaridiosis. From then on phenothiazine base was widely used as an anthelmintic in man, though primarily in veterinary medicine. In some instances, certain toxic reactions have occurred in blood forming organs, somewhat limiting its use in human medicine. However, phenothiazine remains extremely useful as a veterinary anthelmintic agent.

In 1944 the idea occurred to two research groups working in France and in the

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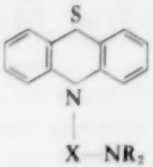
The trademark names for chlorpromazine in their respective countries are as follows: Thorazine (United States); Megaphen (Germany); Hibernal (Sweden); Ampliactil (Argentina); Amplictil (Brazil); and Largactil (France, England, Canada).

United States that some therapeutic properties might be found in phenothiazine derivatives falling under the following formula:



X being a divalent hydrocarbon chain and NR_2 being an aliphatic tertiary amine radical.

In the United States, Gilman and Shirley[4] prepared derivatives of this type while Charpentier[5, 6] synthesized compounds of the same group in the research laboratories at Vitry-sur-Seine. Because of the war, however, Charpentier was unaware of the work being done at the same time by his American colleagues.

The study of the chemical activity of these compounds showed they had very few antimalarial,[7] trypanocidal, or anthelminthic properties and proved disappointing to the two groups working on the project. Consequently, the study of the phenothiazine amine derivatives came to a standstill.

In 1945, however, Halpern and Ducrot in the Rhône-Poulenc laboratories in Vitry started screening the compounds prepared by Charpentier in the hope of finding one with antihistamine properties. Such screening turned out to be successful and quite shortly thereafter their research elicited 3015 R.P. which was recognized as being a powerful antihistamine (III).[8]

This led Charpentier to continue work on the synthesis of basic phenothiazine derivatives with structures similar to those of 3015 R.P. Simultaneously, the physiologic properties and especially the antihistamine properties were studied by Halpern et al. After a few months, the outstanding properties of 3277 R.P., promethazine, were recognized (IV). Clinical studies soon confirmed the laboratory findings and the major therapeutic value of this compound.[9]

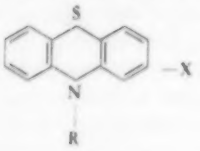
In the meantime, the study of phenothiazine derivatives was carried on in other directions. Bovet and Fournel reported on the vagolytic properties of 2987 R.P. (V) and of 3556 R.P. (VI),[10] both compounds being used subsequently by Sigwald and Durel in the successful treatment of Parkinsonism.[11–13]

Even though clinical studies definitely established the therapeutic value of phenothiazine derivatives in various fields, it soon became clear that some particular side effects could be recognized in treated patients. For instance, in some cases promethiazine caused a marked sleepiness which patients could not always control. Such hypnotic or sedative action could be found in varying degrees of intensity after the administration of other therapeutic phenothiazine derivatives. It should be noted that this was also the case with antihistamine compounds belonging to entirely different chemical groups.

It was interesting to notice that the hypnotic effect of these products appeared to be independent of their experimental antihistamine properties. As a matter of fact, the intensity of these two actions may vary in opposite directions from one product to the next. Furthermore, the hypnotic effect of phenergan, although evident in the

TABLE OF GENERIC AND TRADE NAMES

General formula:



No. in text	No. R.P.	Generic names	Trade names	R	X
I	4560 R.P.	Chlorpromazine	Largactil (Specia) Thorazine (S.K.F.) Megaphen (Bayer) Hibernal (Leo) Ampliactil (Rhodia Argentina) Amplictil (Rhodia Brasileira)	$-(CH_2)_3-N(CH_3)_2$	$-Cl$
II	2955 R.P.	Phenothiazine	—	$-H$	$-H$
III	3015 R.P.	Fenethazine	Anergen (Sumitomo)	$-(CH_2)_2-N(CH_3)_2$	$-H$
IV	3277 R.P.	Promethazine	Phenergan (Specia) Phenergan (Wyeth) Atosil (Bayer) Lergigan (Recip) Fargan (Farmitalia) Thiergan (Astra)	$-CH_2-CH(CH_3)-N(CH_3)_2$	$-H$
V	2987 R.P.	Diethazine	Diparcol (Specia) Latibon (Bayer) Antipar (Farmitalia) Thiantan (Dehydag)	$-(CH_2)_2-N(C_2H_5)_2$	$-H$
VI	3356 R.P.	Isothazine	Parsidol (Specia) Parsidol (Warner) Dibutil (Bayer) Lysivane (M & B)	$-CH_2-CH(CH_3)-N(C_2H_5)_2$	$-H$
VII	3276 R.P.	—	—	$-(CH_2)_3-N(CH_3)_2$	$-H$

clinic, could not be found in small laboratory animals (rats and mice) where this compound acted rather as a stimulant.

Such effects led us to consider the phenothiazine amine derivatives as having some obscure "central" activity. The properties were studied and described by Winter, who reported on the "potentiation" properties of promethazine on the hypnotic activity of hexobarbital in mice,[14] and on the "disorientating" properties of the same product on rats with previously conditioned reflexes.[15*]

* We wish to thank Dr. Winter for informing us, as early as 1950, as to the main results of his work in that field.

In a series of articles published in 1950[16] in another field, Laborit reported on findings in surgery. He considered that some phenothiazine derivatives (promethazine, diethazine) had some beneficial effects in surgical intervention (neurovegetative stabilization, antithermic effect, etc.). These effects were especially noticeable when the substances were administered in conjunction with other materials (pethidine, etc.), capable of acting in other physiologic sites (lytic cocktails).

From these various studies, it appeared in 1950 that the "central" action of phenothiazine derivatives might be of some therapeutic value. In the fall of 1950, a systematic study was initiated with the cooperation of Charpentier for the chemical tests, and Mrs. S. Courvoisier for the pharmacologic tests. The purpose was to study various phenothiazine amine derivatives with a view towards finding a product possessing a high degree of "central" activity regardless of antihistamine activity. The screening tests consisted of the assay of the potentiation of general anesthetics (hexobarbital, ether), the increased activity of analgesics (pethidine, morphine), and the action on conditioned reflexes.

The first series of assays with previously prepared products showed that 3276 R.P. (VII) had a high "central" activity although the antihistamine activity was practically nonexistent.

At that time Charpentier had prepared a new chlorophenothiazine later recognized as chloro-3 phenothiazine.* In view of the results obtained with 3276 R.P., he conceived the idea of branching the same lateral chain on the chlorophenothiazine he had just prepared. On December 11, 1950, he forwarded for physiologic assays a small sample of 4560 R.P. later known as chlorpromazine (I).

From the first experiments it was clear that the new product showed exceptional activity; further work confirmed these findings. (In many respects it has not been surpassed, despite the large number of compounds prepared since 1950.) For this reason when a further study of phenothiazine amine derivatives was continued, a more detailed pharmacologic study of 4560 R.P. was undertaken with the help of Messrs. Fournel, Ducrot, and Miss Kolsky.† By the middle of 1951 this study had progressed to the point where it provided reasonable ground for a first clinical study. After a short and unavoidable trial and error period, chlorpromazine appeared in rapid succession as a first class agent as antiemetic, preanesthetic, and especially in psychiatry.

We shall not dwell here on the therapeutic activity of chlorpromazine. We wish, however, to relate briefly this activity to the multiple pharmacologic properties of the product;[18] we purposely speak of the pharmacologic properties of 4560 R.P. Actually the motives and grounds for the violent controversies which have arisen concerning the mode of action of the product may be related to the fact that too often

* The Beilstein system is used in this paper. In the American studies, which follow the system adopted in *Chemical Abstracts*, the same product is known as 2-chlorophenothiazine.

† Due to various circumstances, the main report could not be published before January, 1953.[17] In that report we tried to give as complete an idea as possible of the experimental facts and to limit to the minimum the interpretation of results. Much earlier, its contents were known to the physicians who tried 4560 R.P. clinically. The same applies to the physiologists whose publications appeared, in some cases, before ours.

authors have tried to explain many clinical effects by a single cause, while such effects are, to some extent at least, relatively independent of each other. This becomes obvious when the pharmacologic activity of a large series of compounds chemically related to chlorpromazine is studied in detail. There are many variations in the behavior of these products in respect to their activity as "potentiator" agents for anesthetic, as antiemetic agents or in respect to their adrenolytic properties, etc. These properties evolve quite erratically from one product to another.

Among all properties exhibited by chlorpromazine in clinic, the most remarkable are those related to psychiatry. However, if we confine ourselves to the action in "potentiated anesthesia" or in "artificial hibernation," we have to recognize that the data obtained through the methods of classic pharmacology do not provide satisfactory explanations. Actually, it has been recognized that the gangliоplegic activity and the decreased metabolism which were first invoked to explain the neurovegetative stabilization are unfounded.

In the same respect we cannot very well subscribe to Decourt's theory[19] which claims that chlorpromazine has a direct depressive action on all animal or vegetative cells; such properties being referred to as a "narcobiotic" activity. This activity is assumed by Decourt to have its origin in an antagonism between chlorpromazine, and hypothetic and not clearly identified enzymes. There is probably some truth in Decourt's theory that chlorpromazine, like many other amines of the same chemical series, has indisputable inhibiting properties on some enzymes,[20] and that other examples of enzyme inhibitions unknown at the present time may be unveiled in the future. It seems, however, that the author of the "narcobiotic" theory drew his observations from wider conclusions than they could reasonably yield, and that the universality of the action of chlorpromazine on the cells cannot be regarded as an established fact.

How then is it possible to relate the clinical effects of chlorpromazine? We spoke earlier of the "central" effects of phenothiazine derivatives. These "central" effects were in fact the very motives of the studies which led to the discovery of 4560 R.P. The vague hypothesis that the presently investigated phenothiazine derivatives acted more or less on the upper nervous centers could not be regarded as scientifically established. However, its likeness was considerably reinforced when various clinicians[21] showed the astonishing effects of chlorpromazine in psychiatry.

More recently, experimental studies have been devoted to the demonstration and study of the action of the product on various encephalic levels. During the past year many highly interesting studies,[22] especially that of G. Werner et al,[23] have tried to pinpoint the "central" action of chlorpromazine which can now be regarded as an established fact. It would, however, be premature to affirm that these studies give a full explanation of what has been observed in clinic. This relative failure was somewhat unavoidable because at that time there was no precise knowledge of the actual physiology and of the functioning of the various parts of the encephalon.

We hope, however, that the knowledge of these physiologic processes will increase in the future. It is even possible that the study of the effects of chlorpromazine and other more or less similar products will cast new light on the functioning of the brain tissues, whether normal or pathologic.

Therefore, we should consider that in the present state of knowledge the origin of the action of chlorpromazine in clinic may be sought in the action of the product on the encephalon, even though such mental processes are still not fully understood.

However, this state of uncertainty should not lead to hesitation in the use of chlorpromazine clinically. We are still ignorant about the mode of action of many drugs currently used in medical fields when such drugs do not act through a direct or indirect effect on parasite organisms (such a term being used in its broader sense). For instance, this is the case with aspirin in its action against headache. Each of us knows its uses from experience but it remains as mysterious now as when the product was discovered.

This is the end of the exposé. We wish only to mention again that the discovery of chlorpromazine, casual as it may be in many respects, remains a memorable experience. It especially shows what can be achieved from teamwork when a group of scientists—chemists, pharmacologists, and physicians—do their best in the hope of some day lightening the burdens of diseases of the body and mind.

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The Pharmacology of Chlorpromazine

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Chlorpromazine is a new synthetic, non-barbiturate central nervous system depressant, which because of its diverse and useful pharmacologic actions,[1] is being used in almost all fields of medicine. Its current applications include the control of nausea and vomiting,[2–4] management of mental and emotional disturbances,[5, 6] and relief of intractable pain.[7, 8] The mounting interest among clinicians to explore further the utility of chlorpromazine in other conditions indicates that a review of its pharmacology would be in order and is, therefore, the motive for this report. Table I summarizes the physical and pharmacologic properties of chlorpromazine.

ABSORPTION AND EXCRETION

Chlorpromazine is readily absorbed whether given orally, parenterally, or rectally. When applied to the mucous membranes it produces local anesthesia similar to cocaine. The fate of the drug in the body is, however, poorly understood. Apparently it is quickly metabolized or deposited in the tissues, for Seibert,[9] using photometric methods, was unable to demonstrate significant drug levels in plasma 20 minutes after giving large doses (150 mg.) to dogs. Determinations in psychiatric patients 90 minutes after the oral administration of 500 mg. revealed drug plasma levels of less than 1 mg. per cent, despite the fact that the patients had been taking daily doses of 2 Gm. for more than a week.

Furthermore, in these patients, less than 1 per cent of the drug was recovered from 24 hour urine samples. In vitro studies revealed that only 40 per cent of chlorpromazine was recovered from liver tissues (dog) incubated for two and a half hours with varying concentrations of the drug.

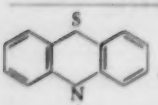
CARDIOVASCULAR SYSTEM

Animals: Giving chlorpromazine in progressively increasing doses to anesthetized dogs produced a sharp increase in pulse rate when levels of 1 to 5 mg./Kg. were reached. Usually cardiac output was not altered significantly until high doses were used, and then it decreased somewhat, in association with peripheral vasodilatation and a secondary reduction in blood pressure. Fall in blood pressure was fairly consistent when doses of 10 mg./Kg. were given, irrespective of change in cardiac output. This decrease, most accentuated immediately after the administration of the drug, was primarily a result of reduced peripheral resistance. This dual reduction of cardiac output and blood pressure is probably due to adrenergic blockade.

Electrocardiographic studies on dogs given 10 mg./Kg. showed some flattening of the T waves in some animals, but alterations were minimal and probably of little

TABLE I

Summary of Physical and Pharmacologic Properties of Chlorpromazine

Physical	Pharmacologic
 $C_{17}H_{19}N(CH_3)_2 \cdot HCl$	1. Depresses central and autonomic nervous systems. 2. Augments the action of central nervous system depressants, such as: anesthetics, sedatives, narcotics, and alcohol as well as mephenesin, curare, and d-tubocurarine. 3. Blocks apomorphine-induced emesis. 4. Alters conditioned reflex in rats. 5. Lowers body temperature and blood pressure slightly. 6. Exhibits slight adrenolytic and weak antihistaminic activity. 7. Relaxes isolated rabbit intestine rendered spastic with barium chloride. 8. Fails to alter the pressor response following central vagal stimulation.
Chemical name: 10-(3-dimethylamino)-2-chlorphenothiazine, usually as HCl Molecular weight: 355.52 Melting range: 193–196 C. Appearance: off white crystalline powder Odor: faintly amine Taste: Bitter; numbing effect on tongue Solubility: Water—one gram per ml. at 26 C. *p*H: 4.9 (5 per cent aqueous solution) somewhat photosensitive	

significance. One dog, however, showed a splintering of the R wave with a widening of the QRS complex and an increase in the QT interval. Larger doses produced marked tachycardia with electrocardiographic evidence of intraventricular block. Definite cardiac toxicity developed when a dose of 75 to 85 mg./Kg. was given over one or two hours; the equivalent of this dose in a man weighing 70 Kg. would be 5,000 mg.

Humans: Chlorpromazine reduces blood pressure in both normotensive and hypertensive patients, regardless of the route of administration. Giving the drug intravenously produces an almost immediate and profound fall in pressure which is lost after two to six hours. After intramuscular injection, the maximum fall in pressure usually occurs 30 to 40 minutes later; with oral therapy, 60 to 90 minutes later. A significant hypotensive response is less frequently observed after oral or intramuscular drug administration when the patient is recumbent. But if the patient stands up, the orthostatic hypotension becomes manifest.

Adrenergic blockade with chlorpromazine is incomplete, since patients given the drug (50 to 100 mg. intravenously) continue to respond to the vasopressor effect of norepinephrine, although nearly twice the usual dose of the pressor agent is required. These conclusions are apparent from the data in table II. Bradycardia did not occur when norepinephrine was administered to patients who previously had been given chlorpromazine.

When chlorpromazine is given at regular intervals for prolonged periods of time, tolerance to the hypotensive effect develops so that after three to four weeks as much as 2 Gm. of chlorpromazine, given orally, will not lower blood pressure significantly in the majority of patients. Since tolerance to the hypotensive response also develops in patients with hypertension, chlorpromazine is of no value for the long term treatment of patients with essential hypertension.

Cardiac output is usually not altered by giving chlorpromazine intramuscularly if the patient is recumbent. However, administering it intravenously produces a sudden peripheral vasodilation followed by an increase in heart rate and temporary increase followed by a decrease in cardiac output. These changes are not marked, being of the same degree as those observed following the administration of ganglionic blocking agents to normals.

These observations are generally supported by Foster and his associates.[10] They found that chlorpromazine given intravenously produced marked vasodilatation in the extremities, a vasodilatation associated with hypotension and tachycardia, which became more marked in the orthostatic position and lasted four to six hours. The more rapidly the drug was administered, the more pronounced were the responses. When injected intra-arterially vasodilatation occurred, apparently a result of adrenergic blockade. It produced an even greater vasodilatation when given intravenously,

TABLE II

Blood Pressure Response to Chlorpromazine and the Effect of Chlorpromazine on the Response to Norepinephrine

Patient No.	Dose and route chlorpromazine mg.	I. Mean blood pressure mm.Hg.				II. Norepinephrine before chlorpromazine			III. Norepinephrine after chlorpromazine		
		Control		Chlorpromazine			Mean blood pressure			Mean blood pressure	
		S	U	S	U	Dose γ/Kg./Min.	Cont	NE	Dose γ/Kg./Min.	Cont	NE
1	25 I.V.	79	84	69	58	.192	83	108	.510	69	85
2	50 I.V.	101	90	70	62	.380	97	125	.471	70	100
3	50 I.V.	103	97	82	55	.260	98	122	.356	82	95
4	50 I.V.	81	85	76	70	.220	85	112	.395	76	94
5	25 I.V.	108	104	116	100	—	—	—	—	—	—
6	60 I.V.	87	87	86	75	.221	90	114	.612	86	95
7	50 I.V.	94	95	87	65	.150	88	120	.311	87	100
8	50 I.V.	85	98	63	52	.278	87	117	.600	63	92
9	25 I.V.	101	97	76	70	.398	101	127	.499	101	94
10	50 I.M.	78	82	80	68	.178	80	114	.321	80	102
11	50 I.M.	95	90	101	95	.254	95	115	.527	101	130
Mean	44	92	92	82	70	.253	90	117	.460	82	99

Key to table: S = Supine.
U = Upright.
I.V. = Drug given intravenously over a 10 minute period.
I.M. = Drug given intramuscularly.
NE = Norepinephrine infusion.
Cont = Observations before norepinephrine infusion.
Mean blood pressure = Direct intra-arterial manometry.

The subjects in this series were given an infusion containing norepinephrine (4 γ/cc.) so as to raise the blood pressure 25 to 30 mm. Hg. They were then given 25 to 50 mg. of chlorpromazine either intramuscularly or intravenously. Thirty to 45 minutes later their blood pressure was again taken, in the upright and supine positions. Norepinephrine was then infused (with the patient supine) rapidly enough to raise the pressure 25 to 30 mm. Hg. again. The difference in the requirement of norepinephrine to raise blood pressure before and after chlorpromazine is indicated in column III.

a fact that suggests additional vasodilatatory responses of central origin, possibly the vasomotor center.

Electrocardiographic studies, conducted in control subjects and in patients receiving the drug therapeutically, showed no definite evidence of irregularities resulting from chlorpromazine (25 to 50 mg.), orally or intramuscularly, in short and long term therapy.[11] Several patients exhibited a minor T wave alteration. One patient, who had diabetic acidosis associated with nausea, vomiting, and hypopotassemia, developed a partial auricular-ventricular block (Wenckebach phenomena) while receiving chlorpromazine therapeutically. Although this persisted for several days, it could never be clearly ascertained whether the arrhythmia was associated with the drug or related to the underlying disease process and low serum potassium. None of the control subjects exhibited electrocardiographic irregularities following chlorpromazine.

RENAL STUDIES

Animals: Our studies on renal hemodynamics, summarized in figure 1, revealed that although blood pressure fell in most animals no significant alteration in glomerular filtration rate occurred. In one instance, however, where blood pressure decreased from 136 to 95 mm. Hg., the glomerular filtration rate decreased from 72 to 48 cc. per minute. Although renal plasma flow frequently varied from period to

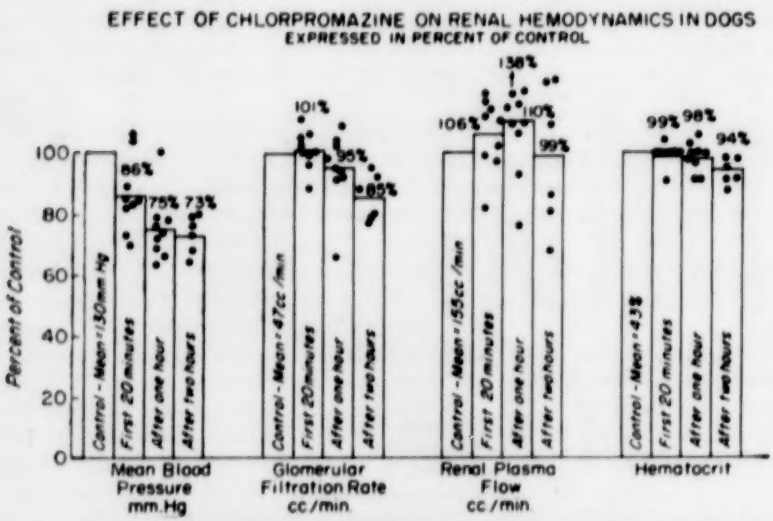


FIG. 1. Effect of chlorpromazine (50 mg., i.v.) on renal hemodynamics in anesthetized dogs. Creatinine was used to measure glomerular filtration rate and para-aminohippurate for renal plasma flow. Mean blood pressure was measured by a damped mercury manometer connected through a manifold to an indwelling arterial needle. Observations were made immediately after one hour and again after one and a half hours. The mean value for the group is expressed as average per cent of control for the group. Each dot (.) represents the value for each animal expressed in per cent of its own control.

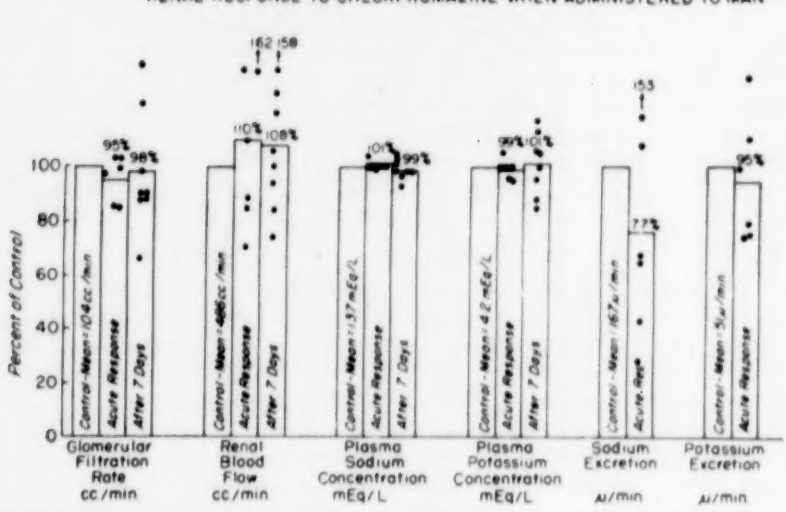


FIG. 2. Effects of chlorpromazine on renal hemodynamics and electrolyte excretion. Acute response = Response one hour after intravenous administration of 10 mg. of chlorpromazine. After 7 days = Response after daily oral administration for one week. The mean values for the group are expressed as average per cent of control for the group. Each dot (.) represents the value for each subject expressed in per cent of his own control.

period after drug administration, this was not a constant response, and if anything, tended to increase. Some of the animals showed a moderate diuretic response associated with an increase in sodium excretion. There was no consistent effect on potassium excretion.

Humans: Differential renal function studies,[11] before and after the acute and chronic administration of chlorpromazine, revealed no consistent alteration of either the glomerular filtration rate or renal plasma flow. No significant changes were noted in phenolsulfonephthalein excretion rates or in urinalyses. Analyses of plasma sodium and potassium showed no appreciable changes in electrolyte concentration after one week of therapy. In contrast to the findings in dogs, there was no evidence of increased sodium excretion. In all probability, the discrepancy is related to the dose given the dogs (3 to 5 mg./Kg.) which was considerably higher than that given patients. The data derived from the renal function studies are presented in figure 2.

CEREBRAL STUDIES INCLUDING HEMODYNAMIC

Cerebral hemodynamic studies, in normal control subjects, employing the nitrous oxide method of Kety and Schmidt[12] showed a decrease in cerebral blood flow in conjunction with a sharp reduction in blood pressure following the administration of chlorpromazine (50 mg., intravenously). However, the arteriovenous oxygen difference increased and, thus, maintained cerebral oxygen uptake. If the blood

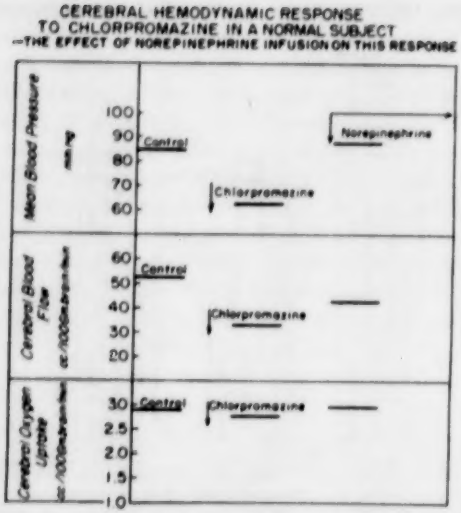


FIG. 3. Effect of chlorpromazine on mean blood pressure, cerebral blood flow, and cerebral oxygen uptake in a typical patient. As the mean blood pressure decreases, cerebral blood flow is reduced but not the oxygen uptake. When the blood pressure is then increased with norepinephrine, cerebral blood flow returns towards the control without altering oxygen uptake.

pressure was increased from the hypotensive levels with norepinephrine, then cerebral blood flow returned to pretreatment levels and cerebral oxygen uptake was not altered. If chlorpromazine was given intramuscularly, the blood pressure was usually not reduced significantly and cerebral blood flow was unaltered. These findings, given in figure 3, show that any change in cerebral blood flow or cerebral oxygen uptake following the administration of chlorpromazine is due to a fall in blood pressure, similar to that produced by giving potent hypotensive agents to normal individuals.

Electroencephalographic studies show that chlorpromazine produces a pattern similar to normal sleep in contrast to barbiturates which produce a rapid rhythm. Terzian[13] has concluded that chlorpromazine depresses the reticular formation, particularly the sensory and autonomic spheres. The central action of chlorpromazine is further evidenced by its potentiation of anesthetics and sedatives.[1]

Chlorpromazine potentiates opiates, anesthetics, and sedatives such as barbiturates. However, in the author's experience, this potentiation is extremely variable. Frequently, there is absolutely no potentiation; whereas in other instances the potentiation may be more than 100 per cent, i.e., the dose of the collateral agent can be reduced by 50 per cent and maintain an equivalent response. Therefore, when chlorpromazine is used for its potentiating effect on opiates, the minimal effective dose of the opiate must again be established by proper dose titration procedure. Tolerance to the sedative and soporific effect of chlorpromazine itself is usually lost after a week or two of continuous administration. Patients who receive the drug regularly for long periods of time frequently complain of inability to sleep at night.

When this occurs, barbiturates are not particularly effective as soporific agents, a rather peculiar pharmacologic response.

The drug apparently inhibits the thermal regulatory center and for that reason has been used for surgical procedures employing controlled hypothermia. When used for this purpose, it helps to prevent shivering, a property common to many adrenergic blocking agents. With this in mind we have employed the drug in the treatment of patients with hyperpyrexia in an attempt to reduce the temperature. We found the drug of little, if any, value for this purpose.

SIDE REACTIONS OF CENTRAL NERVOUS SYSTEM ORIGIN

In high doses (1,600 mg.) chlorpromazine may cause confusion, hyperactivity, and disorganized behavior, but such reactions usually subside a few days after dosage is reduced. A Parkinsonian-like syndrome has been observed in some patients receiving daily doses above 800 mg. In a series of 195 psychiatric patients we observed 14 cases.[14] In 5 the changes were mild: moderate tremor, muscular weakness, stooping posture, and diminution of accessory movements. Another 5 showed more severe changes with typical pill-rolling tremor, some difficulty in articulation, and increased salivation. Four developed a classical picture of post-encephalitic Parkinsonism with masked facies, open mouth, dripping saliva, cogwheel rigidity of the limbs, total loss of accessory movements, and extreme difficulty in articulating, dysphagia, and a typical posture and gait. Oddly enough, in spite of the physical handicaps, these psychiatric patients remained cheerful and their original disease showed no tendency to relapse. In mild and moderately severe cases, reduction of chlorpromazine dosage led to disappearance of the symptoms within a few days. In the 4 severe cases complete recovery was delayed for as long as one month.

RESPIRATORY SYSTEM

Chlorpromazine in small parenteral doses given to normal unanesthetized individuals appears to be a mild respiratory stimulant. However, as the dose is increased, respirations become shallow and irregular. The effect of chlorpromazine on arterial blood *p*H and blood gases is presented in table III. Despite the alterations in respiratory rhythm and depth there is no apparent effect on blood gas exchange in the lungs.

LIVER FUNCTION STUDIES

Studies with chlorpromazine in animals by Courvoisier et al[1] uncovered no evidence of hepatic toxicity. Our studies[11] consisting of thymol turbidity, serum bilirubin determinations, and bromsulfalein tests also failed to show evidence of hepatic toxicity in control subjects or in patients receiving the drug, one or more weeks, for nausea and vomiting. Several of the patients had liver disease prior to receiving the drug. None of these showed any evidence of progressive hepatic dysfunction. However, it was noted that patients with hepatic disease showed an increased responsiveness to the drug and were particularly prone to exhibit sedation, probably as a result of the decreased rate of destruction of the drug by the liver.

TABLE III

Effect of Chlorpromazine on Blood Gases

Patient No.	Arterial O_2* Vol./%		Arterial CO_2* Vol./%		Arterial pCO_2 mm. Hg.		Venous pCO_2‡ mm. Hg.		Hematocrit		Dose and route chlorpromazine mg.
	C	D	C	D	C	D	C	D	C	D	
1	14.0	14.0	48.5	52.2	45	48	59	61	38	39	25 I.V.
2	18.6	19.3	43.8	43.6	41	43	56	45	47	47	50 I.V.
3	18.3	19.0	38.4	37.3	38	35	45	47	45	47	50 I.V.
4	16.4	15.4	49.5	50.8	44	44	57	52	41	37	50 I.V.
5	16.9	16.6	38.3	45.1	—	—	—	—	44	43	25 I.V.
6	14.7	14.7	50.2	49.8	44	39	49	49	39	36	60 I.V.
7	20.2	19.5	43.8	47.0	32	40	43	56	52	50	50 I.V.
8	16.1	15.6	49.5	51.3	46	51	56	56	41	39	50 I.V.
9	18.1	18.1	43.9	45.6	46	45	58	58	47	47	25 I.V.
10	16.7	17.1	41.0	42.3	37	37	46	48	46	46	50 I.M.
11	16.2	15.0	42.0	40.0	36	32	44	42	44	43	50 I.M.
Mean	16.9	16.8	44.4	45.9	41	41	51	51	44	43	44

Key to table: C = Control observation.
D = Observations made 30 to 45 minutes after the parenteral administration of chlorpromazine.
I.V. = Intravenously.
I.M. = Intramuscularly.
* = Arterial blood taken anaerobically from femoral artery.
‡ = Venous blood taken anaerobically from jugular bulb.
pCO_2 = Partial pressure of CO_2.

Despite the absence of hepatic damage in controlled studies, jaundice has been observed fairly frequently. Kelsey and his associates[15] have reported on 20 cases. The dosage of chlorpromazine in these cases is interesting in that it varied from 40 mg. per day for five days to 24,000 mg. given over a period of 30 days. Choluria and clay-colored stools were noted in all but 1 patient. Extreme pruritus was another common finding. Hyperpyrexia for a very brief period was observed in 5 of the 20 patients. Splenomegaly was absent in all patients but 1; hepatomegaly was present in 11.

Other concurrent effects seen in 13 of the 20 patients were nausea and vomiting, hypotension, myalgia, and anorexia without nausea. Epigastric tenderness was seen in 1 patient and drowsiness in another.

The duration of toxic hepatitis is difficult to determine because of the shortness of follow-up. Clinical recovery occurred in all 20 patients, although abnormal hepatic function, as determined by laboratory studies, persisted in many. The two longest periods of abnormality were found in a patient who had previously had a cholecystectomy but normal initial liver function tests, and another patient who had a previous diagnosis of cirrhosis of the liver. These 2 cases may represent a continuation or exacerbation of underlying disease.

Liver function abnormalities presented a characteristic picture. The serum bilirubin was moderately elevated from 1.9 mg. per cent to a maximum of 12 mg. per cent in all cases. The cephalin flocculation tests were normal except in 2 cases. Thymol turbidity was normal except in 3 patients, being 8.0, 17.9, and 22.0 units, respectively, in these cases. The alkaline phosphatase values were definitely elevated to levels that are considered indicative of biliary obstruction in all patients. Albumin-globulin ratios were generally normal, indicating the absence of severe underlying chronic liver disease. Urobilinogen was present in abnormal quantities. Prothrombin activity was depressed in 3 patients and normal in the remainder. Of particular interest was the fact that blood urea nitrogen, which was studied in 10 patients, was found to be elevated in all but 2. An attempt was made to correlate clinical and laboratory features with the pathologic findings in the 7 cases in whom liver biopsies were taken. The cases appeared to show 3 types of histologic alterations.

Type 1. This type showed clinical evidence of parenchymal liver damage as indicated by the presence of elevated thymol turbidity and a prothrombin deficiency. In addition, there was moderate elevation of the alkaline phosphatase. The pathologic findings were indistinguishable from those of acute hepatitis. There were polymorphonuclear leukocytes, lymphocytes, and plasma cells infiltrating the periportal areas.

Type 2. This was the most common clinical type. These cases presented a clinical picture indistinguishable from obstructive jaundice in that there was always a moderate elevation of the alkaline phosphatase. None of the laboratory tests of parenchymal liver damage were abnormal. The illness was mild and there was prompt clinical recovery. The pathologic findings were those of diffuse inflammatory change associated with bile stasis and some evidence of liver cell regeneration.

Type 3. There were 2 patients who represented a type in which the clinical symptoms were more severe and prolonged. In 1 patient the laboratory tests for parenchymal liver damage were positive but had been normal prior to chlorpromazine therapy. Neither case showed a tendency toward reversal of the serum albumin-globulin ratio. Interestingly, both cases showed marked azotemia. The presence of abnormal serum protein was indicative of chronic liver disease and compatible with the pathologic findings of early cirrhosis.

GASTROINTESTINAL TRACT

Chlorpromazine inhibits gastrointestinal motility by its effect on the autonomic nervous system[1] as well as by its direct inhibitory effect on smooth muscles. In vitro studies revealed that chlorpromazine relaxes isolated rabbit intestine rendered spastic with barium chloride. When chlorpromazine is given to patients in large doses it produces rather marked constipation as a side reaction. Otherwise, no serious side reactions of gastrointestinal origin are known to the author. The effect of gastric secretions has not been well worked out as yet.

HEMATOPOIETIC SYSTEM

Studies including red and white blood cell count, hemoglobin determination, and a differential count in patients who took chlorpromazine (25 mg., orally, four

times a day) showed no evidence of hematopoietic disturbances. Toxic granules were observed in the leukocytes of one subject, but the significance of this observation is not known. We have also seen 1 patient who developed agranulocytosis and died, while receiving in excess of 1,000 mg. a day.

TOXIC SKIN MANIFESTATIONS

Dermatitis appeared in 27 cases out of 412 being treated with relatively large doses (1,000–1,600 mg. per day) of chlorpromazine. In 2 the rash was of a maculopapular type. In 6 the area of distribution included the whole body. In others it was confined to the arms, particularly extensor surfaces, chest, neck, and forehead. Pruritus was marked. Two patients showed a generalized erythema multiform. One exhibited a localized nodular eruption on the phalanges, another patient developed an acniform eruption over the face with painful lesions on the gums and palate. Two patients suffered with a generalized exfoliative dermatitis. One was severely ill with high fever and delirium. He responded to ACTH.

Most, but not all, of these individuals gave a history of allergic response to other drugs, foods, etc. The dermatitis typically became manifest during the second week of treatment. Only 2 patients who developed dermatitis were receiving less than 100 mg. daily; above this level there was no correlation between dosage and incidence of dermatitis. No local skin reactions were noted at injection sites aside from induration with reddening of the overlying skin.

Following cessation of chlorpromazine the rashes usually cleared within one week. In a few patients pruritus persisted, particularly if the patient exposed himself to sunlight. Recently we observed that the rash often disappeared spontaneously despite continued drug administration. Pyribenzamine usually afforded adequate relief of the pruritus in those patients. Oddly enough, in those patients in whom chlorpromazine had been stopped, re-institution of therapy after the skin had cleared did not lead to recurrence of the dermatitis in some patients.

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Chlorpromazine in Internal Medicine

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Chlorpromazine, because of its versatility, is useful to the internist in a variety of conditions (1) for relieving nausea and vomiting, (2) for controlling intractable hiccoughs, (3) for treating psychosomatic problems such as anxiety and superficial neuroses, (4) for managing pain by potentiating the action of narcotics, sedatives, and hypnotics. The current communication is a general estimate of the possible applications of this drug as a therapeutic agent in internal medicine. The results herein described should be considered qualitative inasmuch as the drug has not been evaluated over a sufficiently long period of time to draw quantitative deductions. This is particularly true when applied to the area of psychosomatic medicine. Only long term follow-up will allow an accurate appraisal of the lasting benefits to be gained by chlorpromazine in an area of therapeutics in which evaluation of results is fraught with difficulties.

THE TREATMENT OF NAUSEA AND VOMITING

Dosage: Adult patients require 10 to 50 mg. doses, orally or intramuscularly repeated as needed to control symptoms. Usually we employ an initial oral dose of 10 mg. in patients who are moderately nauseated but not actively vomiting. If nausea persists we then increase the dose to 25 mg. When vomiting is present we give an initial dose of 25 mg. and restrict the patient to a nonambulatory status to minimize the transient hypotensive and sedative effects that occur during the first few days of therapy. If nausea and vomiting are not controlled within three hours after the 25 mg. dose, increase the dose to 50 mg. and repeat as necessary to control symptoms. In many instances we found that patients distressed with intermittent vomiting were unable to retain oral medication for a sufficient length of time to allow adequate absorption of the drug. Under these circumstances the first dose must be given parenterally by deep intramuscular injection, or rectally, in suppository form. When giving the drug intramuscularly a step-wise procedure with regard to dosage is followed; start with small doses and increase them until a dose level which controls symptoms is reached. Once nausea and vomiting are arrested, switch to oral medication, tablets or syrup, unless it is not possible for reasons other than nausea and vomiting. In such instances the drug can be continued by intramuscular or rectal administration.

Some patients periodically required upward adjustment of their dosage as they developed tolerance. Others began to vomit when they awoke in the morning as the effect of the bedtime dose wore off. When vomiting recurred, giving the first dose of the day either intramuscularly or rectally (suppositories) checked it. Breakthrough of drug effect can be avoided by having the patient take an early morning (2 a.m.) dose.

RESULTS IN THE TREATMENT OF NAUSEA AND VOMITING

Table I summarizes results with chlorpromazine used as an antiemetic in the treatment of 230 patients. The results were evaluated as follows: excellent in those cases in whom vomiting stopped and the nausea was completely relieved; good when vomiting stopped although nausea persisted; fair when vomiting stopped but slight nausea continued, and failure in those cases unrelieved by chlorpromazine. Placebos were substituted whenever there was a question of psychic versus drug effect. All patients were actively vomiting prior to chlorpromazine administration. The cases studied represent a wide range of causes for nausea and vomiting including that induced by drugs, infections, toxemias, gastrointestinal disturbances, and cardiovascular disease. Findings on 77 patients who experienced nausea and vomiting associated with drug therapy show that chlorpromazine is extremely effective in such instances.

Of 40 patients being treated with nitrogen mustard, in only two instances did chlorpromazine fail to arrest the nausea and vomiting, 5 patients remained quite nauseated but did not vomit, and 9 experienced nausea intermittently.[1] Chlorpromazine was equally effective, whether given prophylactically or therapeutically. It was less effective orally when the patient was already nauseated and /or vomiting. However, if nausea and vomiting were first arrested by giving the drug intramuscularly, the patient could usually be continued on oral medication satisfactorily.

Chlorpromazine proved to be an effective agent for combating nausea and vomiting due to gastric irritation resulting from aminophylline and antibiotic therapy.

TABLE I

Summary of Results with Chlorpromazine in Treatment of Nausea and Vomiting Due to a Variety of Causes in 230 Patients

Etiology of nausea and vomiting	Number patients	Therapeutic response			
		Excellent	Good	Fair	Poor
Digitalis therapy	6	6	0	0	0
Hexamethonium therapy	3	0	3	0	0
Nitrogen mustard therapy	40	24	9	5	2
Urethane therapy	2	1	0	1	0
Antibiotic therapy	10	6	4	0	0
Narcotics	6	6	0	0	0
LN51	1	0	1	0	0
Quinidine therapy	2	0	1	0	1
Aminophyllin therapy	6	4	1	1	0
Aminopyrine therapy	1	0	1	0	0
Totals	77	47	20	7	3
Infections	45	36	6	1	2
Toxicosis	49	34	9	4	2
Cardiovascular	8	7	1	0	0
Gastrointestinal	32	24	3	4	1
Miscellaneous	19	12	5	0	2
Totals	230	160	44	16	10

While very successful for controlling nausea and vomiting associated with morphine administration, chlorpromazine has not proved effective in preventing nausea and vomiting following the administration of Veratrum.[2]

Chlorpromazine also appears to be an effective antiemetic agent when patients are distressed by the nausea and vomiting that come with infections and toxic reactions from systemic diseases of the noninfectious varieties. Although it provides symptomatic relief of nausea and vomiting, the drug has no effect on concurrent manifestations such as weakness, diarrhea, and fever. Only 2 of 26 patients with infectious gastroenteritis failed to respond to the antiemetic effect of chlorpromazine.

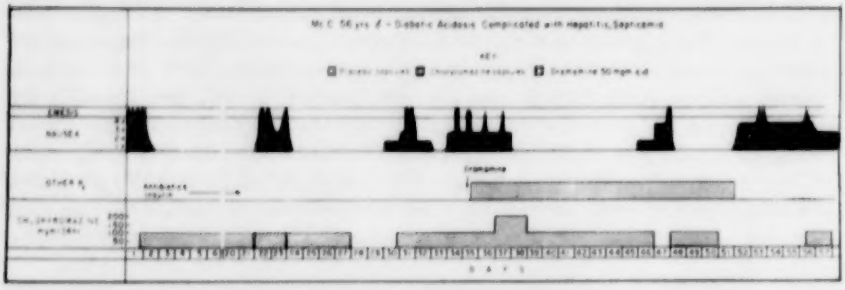

FIG. 1. Response in a patient with nausea and vomiting due to diabetic acidosis complicated by infection. Initially adequate control was maintained with 25 mg. given four times a day by mouth. At one period after vomiting was arrested, the drug was discontinued. Vomiting recurred and then the previous dose of chlorpromazine proved inadequate. Dramamine also proved to be ineffective. The dose of chlorpromazine was increased to 50 mg. which arrested the nausea and vomiting. The dose was then reduced to the previous 25 mg. dose, given four times a day, without recurrence of nausea and vomiting. (Courtesy Am. J. M. Sc.)

Nausea and vomiting associated with systemic diseases (toxicosis) as metabolic disturbances, malignancy, and renal failure also yielded to chlorpromazine. In renal failure small doses produce a pronounced effect, apparently due to reduced drug excretion. Patients with hepatic disease likewise appeared to be more responsive to the drug than did patients with normal hepatic function. In 6 of 9 patients to whom chlorpromazine was given, nausea and vomiting associated with peptic ulcer were relieved. This may be due to the local anesthetic effect of the drug or to its central antiemetic effect. Of particular interest is the fact that vomiting associated with intestinal obstruction is frequently blocked by chlorpromazine. This makes it imperative to determine the cause of vomiting before instituting chlorpromazine therapy since otherwise a serious pathologic condition may be obscured.

Side Reactions. In evaluating the side effects from chlorpromazine, when used in the treatment of nausea and vomiting, we found that approximately half of the patients studied reported varying degrees of drowsiness, 25 per cent developed dizziness, and 20 per cent developed a slight drop in blood pressure. There was no evident relation between the cause of vomiting and the development of side reactions. Drowsiness was very mild in most cases and would not interfere with the patient's normal activity. Some, however, were markedly affected. Sedation was most

marked during initial treatment, subsiding a considerable degree within a few days as the drug was continued. In patients who experienced marked sedation, reducing the dose often remedied the situation without altering the antiemetic effect. If drowsiness persisted, in spite of lower dosage, it could usually be controlled by giving d-amphetamine (Dexedrine) sulfate 5 to 10 mg. concurrently.

The resulting dryness of the mouth is more annoying than serious. The fall in blood pressure is mild in most cases and accompanied by a compensatory tachycardia, usually 10 to 20 beats a minute. In 7 patients, however, a fall in pressure of 30 to 40 mm. Hg. occurred, a fall that was orthostatic in nature. In 3 cases the pressure went as low as 90/60 mm. Hg. A maculopapular skin rash occurred in 1 patient. However, the side effects associated with the antiemetic use of chlorpromazine are generally of minor concern. Although we observed no evidence of gastrointestinal or hepatic dysfunction in our series, we have had a number of patients with jaundice associated with chlorpromazine therapy referred to us for study. The jaundice in such patients usually subsides when the drug is withdrawn.

USE IN THE TREATMENT OF INTRACTABLE HICCOUGHS

A series of patients with intractable hiccoughs who failed to benefit from commonly used remedies were given chlorpromazine. The hiccoughs were associated with severe heart failure, carcinoma, and conditions following genitourinary surgery. In most patients hiccoughs were arrested within 30 minutes after a single 25 mg. dose, given intramuscularly. A few required an additional dose of 50 mg. to control their hiccoughs. A typical response is seen in figure 2. Only 2 of 16 did not respond to the drug.

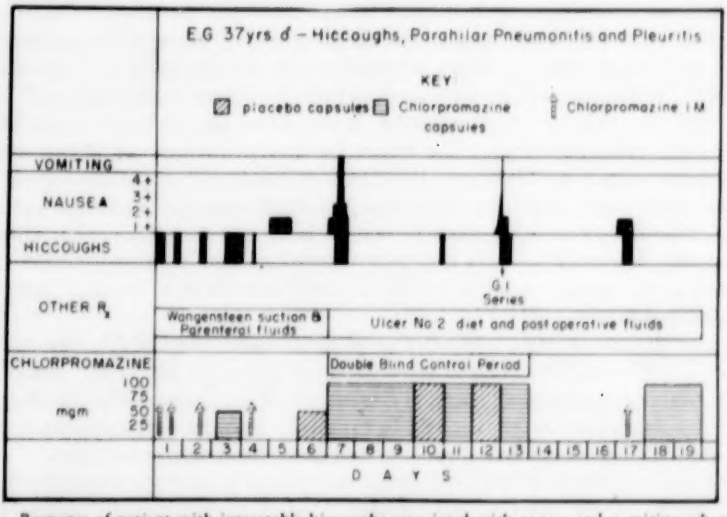

FIG. 2. Response of patient with intractable hiccoughs associated with nausea and vomiting when given chlorpromazine. Hiccoughs recurred when a placebo was substituted for chlorpromazine on several occasions. (Courtesy Am. J. M. Sc.)

USE OF CHLORPROMAZINE FOR POTENTIATING NARCOTICS AND OTHER CENTRAL NERVOUS SYSTEM DEPRESSANTS

Sadove and his associates[3] found that chlorpromazine, plus narcotics, relieved pain in patients who could no longer be made comfortable with large doses of narcotics alone. These investigators observed that patients, some of whom stated that their pain was not appreciably altered, spoke of it as an objective phenomenon, that is they no longer minded the pain, even though it was still present. Lucas et al,[4] in treating advanced cancer patients, reported relief of pain and a reduction in the need for narcotics.

In our experience variable results have been obtained with chlorpromazine to augment the action of analgesics and sedatives. In some cases the potentiation is marked, while in others it is practically nil. For this reason it is best to limit the initial dose of chlorpromazine to 25 mg., orally or intramuscularly, in conjunction with one half the usual dose of narcotic or sedative. Dosage can then be adjusted, upward or down, to suit the individual response. Patients generally can be kept comfortable on doses given every four hours. Exceeding a dose of 100 mg. seldom increases effectiveness. If tolerance develops it can be overcome by discontinuing the drug for a brief time and later reinstituting its use intermittently.

TREATMENT OF PSYCHOSOMATIC AND MINOR EMOTIONAL DISTURBANCES

One hundred eleven patients who presented one or more features of tension as their chief complaint were treated.[5] Nervousness, irritability, fatigue, headache, indigestion, muscular aches and cramps, insomnia, anorexia, and inability to concentrate were common symptoms prior to administering the drug. Almost all of the patients had previously been treated in other ways. Seventy-eight patients obtained excellent results, 9 patients obtained no benefit and in 24 the response was only fair. With some, relief was immediate; others required manipulation of dosage for best effect. Contrary to expectation, it was found that patients often obtained more benefit from small doses. The reason for this is that doses of 50 mg. or more, taken three times a day, bothered these patients with side effects causing them to discontinue therapy. Side effects were minimal when doses of 15 to 30 mg. were used. Many patients were on a regular schedule at first, but they later took chlorpromazine only as needed to meet emergency situations that increased tension states. Failures in this group occurred mainly in patients with fixed somatic complaints and immature personalities.

Typical anxiety neuroses responded in much the same way as did tension states, that is, good to excellent results were obtained in two thirds of the group. Improved sleeping, increased appetite, and reduction of nervousness were the first signs indicating that a good response could be expected. Poor results or failures appeared to be associated with extreme chronicity and fixed somatization reactions.

Relief of depression and associated symptoms occurred in 28 of the 38 patients treated. Three others, whose response was graded good, felt considerably better, gained weight, slept, and took more interest in their affairs. The 7 patients who obtained a poor result either failed to respond or were obliged to discontinue the drug because

of side effects. Patients with chronic coversion hysteria of the paralytic variety failed to show a favorable response to small doses of chlorpromazine.

Thirteen schizophrenics, most of whom were chronic cases leading a secluded life outside the hospital, were treated. All experienced marked relief from annoying symptoms, particularly those associated with tension. A relapse promptly occurred when they discontinued the drug. Two of this group having had acute schizophrenia of a few days duration and exhibiting bizarre behavior with florid delusions and hallucinations, responded so well that hospitalization became unnecessary. Symptoms of the illness in both patients disappeared within a month.

Migraine attacks were considerably alleviated. Of the three migraine sufferers treated, two obtained more relief and had fewer attacks when taking small doses of chlorpromazine, along with salicylates, than with any other medication. The other patient who had infrequent but severe migraine attacks was given 50 mg. intramuscularly when the onset of visual disturbance occurred. She then slept for several hours and awoke refreshed and free of headache. Standard treatments given previously had failed to give more than slight symptomatic relief.

Six epileptics had fewer seizures when chlorpromazine was combined with standard anticonvulsants. Three have been free of seizures since starting this medication. Along with the decrease in the number of seizures there has been an increase in general well being. Also, some of the patients felt they could work more effectively. One patient developed minor seizures in place of grand mal attacks. We have also tried chlorpromazine for the therapy of the dumping syndrome following gastrectomy, but so far it has proved ineffective.

SUMMARY AND CONCLUSIONS

Chlorpromazine is an effective agent in treating nausea and vomiting due to numerous causes. It potentiates analgesics, sedatives, and hypnotics but the degree of this response is extremely variable and the effective dose of the collateral agent must be re-established for each patient after the chlorpromazine is added to the therapy. It shows promise as a therapeutic agent in psychosomatic medicine. However, its place in this sphere has not been fully evaluated as yet and, therefore, conclusions cannot be drawn until evidence confirming the preliminary results is forthcoming.

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Neuroleptic Effects of Chlorpromazine in Therapeutics of Neuropsychiatry*

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Chlorpromazine, considered first as a ganglioplegic, then as a potentiator, and finally as a "neuroplegic," has shown itself to be a drug of first importance as a modifier of the nervous system, especially of the central and peripheral neuroautonomic system. Since the beginning of 1952, the applications of this compound have rapidly extended to all fields of medicine, surgery, and obstetrics. However, the neuropsychiatric indications remain among the most important.

In our specialty, the drug is used according to various methods and conceptions. It may have something to do with the present increase in interest which is now shown in Europe concerning sleep treatment, introduced to psychiatric therapy by Klaesi some 30 years ago and brought up to date by the use of chlorpromazine in combination with barbiturates. Furthermore, as a consequence of the work of Laborit on artificial hibernation by neuroautonomic disconnection, certain investigators conceived the idea of applying this principle in neuropsychiatry.

In 1952 we studied this question and soon learned that complete hibernation, such as that practiced in surgery for instance, would have extremely limited applications in psychiatry. On the other hand, chlorpromazine by itself, as a component of the "lytic cocktail" of Laborit, seemed to offer such important possibilities in mental and nervous pathology that we have used it alone in prolonged and continuous administration. The results were such that we have adopted the method under the name neuroplegic treatment, or better, neuroleptic treatment.

NEUROLEPTIC TREATMENT

By the very nature of its continuity and duration, the neuroleptic treatment is linked to the principle of hibernation therapy, at least as far as it is opposed to shock treatments, which could be called "the body alert in its most intense form."

METHOD OF TREATMENT

Our technique is extremely simple and is currently utilized in numerous psychiatric hospitals. The neuroleptic treatment can be administered in three ways:

1. *Intramuscular injections of chlorpromazine:* We have recommended this method to obtain continuous action. Three injections every 24 hours are made, when the patient wakes up, after the midday meal, and at bedtime. The treatment is started by one injection of 50 mg., which gives an idea of the reactions of the patient, and increased to 100 to 200 mg. daily with an average of three injections of 50 mg. per day.

* Translated from the French by Paul H. Pazery, Philadelphia, Pennsylvania.

In principle, the duration of treatment is not limited. It depends on the gravity of the psychosis and its therapeutic evolution. Intramuscular administration is continued for an average of two to four weeks, when oral administration is substituted.

2. *Oral administration:* The doses are regularly spaced during the day. In this case the doses are larger, 200 to 250 mg. per day. The oral route can be utilized from the start, as we do in certain departments treating neuroses, or following a series of injections. In any case, the doses indicated above require strict bed rest at the start and regular medical supervision, that is they can only be administered within the confines of the hospital.

3. *Ambulatory or outpatient administration:* This method can be used in very light cases on condition that the patient remains in his room at least during the first week of treatment. Oral administration alone should be used; 100 to 150 mg. should be administered per day in four to six doses of 1 tablet of chlorpromazine. The treatment should last at least two to three weeks and, if desired, doses can be decreased progressively as symptoms disappear.

In general, we abide by the following rules: The entire amount required is given on the first day. We do not give progressively increasing doses because, therapeutically, one should not underestimate the necessity of inducing immediate neuroplegia.

It is especially important to assure continuance of the treatment as certain reactions can appear if this continuity is not observed.

One should not hesitate to prolong treatment long after the disappearance of symptoms when their disappearance was progressive as it is impossible to predict the duration of treatment since this depends on the seriousness and evolution of each case. Three to six weeks constitute the average length of treatment. In cases of relapse after the treatment has been discontinued, there should be no hesitation to reinstate it even for months, in serious cases.

The matter of duration of treatment might also explain the differences in posology recommended by various early French publications, on the one hand, and the large doses recommended by many authors in America, on the other. The latter do not hesitate to make use of daily doses of 600 to 900 mg. and more, probably with the intention of obtaining better results more rapidly from the very beginning.

The neuroleptic treatment is no more a sleep treatment than it is an artificial hibernation. Occasionally, the patient goes through a phase of initial somnolence, but he soon finds himself in a very characteristic mental condition that we have called the psychic syndrome of chlorpromazine: "The apparent indifference and delay in response to outside stimulation, the emotional and affective neutrality, the decrease in initiative and preoccupations, without modification of consciousness or of intellectual faculties" constitutes that syndrome. H. E. Lehmann of Montreal, confirming these data, gave us an objective demonstration by test methods.

At the same time one observes marked neuroautonomic modifications. The most characteristic are paleness of the face, dryness of the mouth, and variations of the pulse and blood pressure. The latter are related to the blocking of the orthostatic reflex, always observed by us, together with Y. Tardieu. This justifies the rule of bed rest, at least as long as the effect lasts.

The treatment has an antithermic effect on febrile patients. In others one can observe a slight initial hypothermia. In the process of treatment made with large doses, there are, in the temperature curves, high points lasting a few hours. These are indicative, not of infection, but of modifications in thermic regulation. The hematologic disturbances, among them a drop in the eosinophils, are purely initial and transitory. We have never been able to find, even after the longest treatment, any alterations in the red or white blood cell counts, or evidence of hyperleukocytosis, as are observed after the sleep treatments.

INDICATIONS AND RESULTS

The psychiatric applications of treatment by chlorpromazine have increased since our original investigations were made three years ago. Today our knowledge is based on almost 1,000 patients treated. The results we have obtained have been the object of a series of publications where the main indications are given in full detail (see bibliography). The most important indications remain those first outlined, they are mental disturbances of considerable seriousness. However, the effect of the treatment is not merely symptomatic. It has a real curative effect in a certain number of cases.

States of excitation and agitation are fundamental indications of this therapy. The most remarkable effect is, without doubt, the change which has taken place in the entire atmosphere of these hospital wards. In a few hours, in a few days at the most, the patients are calmed without being somnolent. Today the neuroleptic treatment is the treatment of choice in manic states, usually little influenced by electroshock or sleep treatment. Phases of excitation which characterize the evolution of psychoses and periods of agitation in schizophrenics are nearly always controllable. Aggressiveness and impulsiveness are symptoms which are generally favorably influenced.

Mental confusion, acute and subacute psychoses, even if accompanied by fever and hyperazotemia, react remarkably well. The rapid action of the drug in states of mental confusion is noteworthy. Subacute alcoholic reactions deserve special mention since they can be stopped if action is taken early enough. Strychnine in its usual doses can be combined without danger.

States of anxiety, depression, and melancholia react differently. Anxiety nearly always responds remarkably well to the action of chlorpromazine. It can cure simple or neurotic depressions and certain melancholias, especially presenile melancholias. True melancholia, wherein anxiety and insomnia are relieved by chlorpromazine, often remains an indication for shock treatments, but the number of electroshocks can be decreased by concomitant use of the neuroleptic treatment. The latter treatment can have a preventive effect, or more exactly an abortive effect, if it is applied at the beginning of the manic-depressive psychosis.

Concerning delirious and hallucinatory psychoses one might say that transient "episodes of delirium" like certain protracted periods of delirium are often reduced just as easily by chlorpromazine therapy as they are by electroshock. Hallucinatory psychoses and chronic delirium react much less favorably, though extended use of

the treatment in psychiatric institutions has shown remarkable improvements in severe, chronic cases.

Schizophrenia often requires a special posology. It may be necessary to administer double doses, or doses twice as large as those we have previously mentioned. The phases of agitation or anxiety can be reduced, as can also impulsiveness and aggressiveness when they are present. But most important, in the great majority of cases it is the improvement in the rapport of the patients which opens up new possibilities for psychotherapy and ergotherapy. Such improvements are noted in the diverse forms of the disease which include the paranoid form, although one cannot speak of complete cure. Insulin therapy, nevertheless, is still very valuable in many indications. In regard to the application of this treatment in the field of psychoneuroses, it would seem that anxiety neuroses and phobic neuroses react infinitely better than obsessive neuroses.

Patients suffering from psychasthenia experience an improvement in their depressive symptoms, in their anxiety or hypochondria, rather than in the asthenia itself, which may be aggravated.

Neuroses of insomnia react very well to chlorpromazine, either used alone or with Phenergan or barbiturates. The somatic manifestations of hysteria and the hypochondriac syndromes of various origins, usually so discouraging for the physician, are often very much improved by the neuroleptic treatment.

This led us to treat the so-called psychosomatic disorders, which we limit to the disturbances appearing in neurotic individuals as a result of a visceral miopragia, itself frequently related to neuroautonomic disorders. In this case, the neuroleptic treatment is doubly effective acting on the psyche on the one hand and effectively reducing the somatic manifestations on the other. This led us to report the results obtained in arterial hypertension associated with great anxiety, in ulcerous syndromes brought about by afflicting preoccupations, in obsessive neurodermatitis, and in the postoperative dysurias of neuropaths. The painful spasmodic manifestations accompanied by pruritus or irritation in obsessed, anxious or pusillanimous neurotics are a fairly vast field of application.

In a general way it can be said that the treatment has a good effect on psychopathologic states accompanied by an increase in nervous and mental tension, and less effect on those accompanied by a decrease of psychologic tension, such as psychasthenia. Before considering more recent neurologic indications, it is necessary to discuss the relation of the neuroleptic treatment to sleep treatments and to artificial hibernation.

Concerning the psychoses, a comparison of the results obtained by various authors is very clearly in favor of chlorpromazine used alone. Manic states, for instance, frequently recur after sleep treatment, while chlorpromazine has truly changed the atmosphere of the psychiatric wards for agitated patients and has eliminated the need for methods of restraint.

In the treatment of neuroses, one must realize it is important to make the patients sleep in order to put an end to their preoccupations. Frequently, however, it is sufficient to induce a sleep of short duration by adding very small quantities of barbiturates to help the patient accept his treatment. In the final analysis the results

appear to be as good as those obtained with a prolonged sleep treatment without the serious drawbacks of the latter. The prolonged sleep treatment, nevertheless, has its indications, particularly during the detoxification of drug addicts and in some cases of paranoia or hypersthenic hypochondriacs.

It seems to us that artificial and complete hibernation, as proposed by Laborit, has its indications in the rare and extremely serious cases of our specialty: acute delirium at its height, confirmed delirium tremens, and post-therapeutic coma in the Sakel cure. Equally interesting are the indications of the shock treatments and of the treatment which is designed to put the nervous system at rest.

Considered from this aspect, the case of manic-depressive psychosis is remarkable: Chlorpromazine has become the treatment of the manic episode, in the same way that electroshock has become the treatment of the depressive phase. The results obtained by seismotherapy were as irregular in mania as those of chlorpromazine were in depression. The association of these methods is possible and in many cases necessary. It would seem that the number and the intensity of the shocks can be decreased in those patients suffering from melancholia if they have been treated with chlorpromazine. Three or four treatments with electroshock, even intravenous injection of magnesium sulfate, associated with the neuroleptic treatment are often sufficient to bring an end to the melancholia.

NEUROLOGIC APPLICATIONS

Although these applications have less scope, they are extremely important from the point of view of neurophysiology.

The various choreas offer an interesting field. Chlorpromazine would seem to have an outstanding curing effect on Sydenham's chorea. However, we prescribe anti-infectious medication with it. In chronic choreas one generally obtains a symptomatic effect which is not negligible. In Parkinsonism, chlorpromazine does not have any curing action, though Canadian investigators have shown that the rhythm of the tremors and the stiffness is always reduced. This is an important factor in understanding the neurologic action of the drug.

The Italians have noted good results in the treatment of hemiballism and spasms of torsion. We have also had good results in certain patients affected by tics.

Concerning epilepsy, the drug seems to have no effect on convulsive seizures though spectacular results have been reported in the treatment of confused states. M. David and his co-workers have recommended chlorpromazine used intravenously in epileptic states. This is comparable to the effect of artificial hibernation on eclampsia. Artificial hibernation has been proposed in the treatment of coma resulting from carbon monoxide and even in cases of coma caused by barbiturate poisoning (H. Benard).

The application of the neuroleptic treatment applied to pain remains to be considered. Many tests now being made in France and the United States seem most encouraging even in pain of cancer.

INCIDENTS AND REACTIONS OF THE TREATMENT

Narcotherapy, as recommended by Swiss investigators, presented dangers attributed to the prolonged intoxication caused by the drug. Modern sleep treatments made with potentiated drug combinations are less toxic but, nevertheless, do not completely eliminate the drawbacks of prolonged sleep which are far from being negligible. These reactions do not occur during neuroleptic treatments probably because the sleep they induce is normal. The very few cases of infection, noted in our first publications and ascribed to the antiphlogistic action of the drug, have never occurred again. The main reactions were ascribed to postural hypotension during the first days if the patients got up prematurely. These reactions are easily overcome by making the patient lie down and justify bed rest. Neuroautonomic disorders such as tachycardia and palpitations may, in certain neuropaths, require administration of small doses of sedatives for short periods. The acidity and the irregular resorption of the injectable drug may cause minor local irritations, but no abscesses.

When this treatment is used on a large scale, it has one drawback which should not be underestimated: reactions of the skin and the mucosa affecting the nurses handling chlorpromazine. These occur more frequently in women than in men, and probably more often in individuals already affected with allergic reactions. They consist of acute and subacute eczema of the face and hands, in blepharitis, all reactions which appear early on sensitive individuals and which have never been seen after a period of prolonged use. One seasonal factor due to photosensitivity has been noted. This seems to occur especially in the injectable form of the product.

Among the rare reactions also attributed to chlorpromazine, one must mention hepatitis and vascular accidents. Hepatitis especially has been observed on the American continent though we have only seen 2 cases of it out of 1,000 patients treated. It has been observed more frequently by the Swiss authors, who make use of large doses of chlorpromazine, and it is probable that the amount given influences the occurrence of hepatitis. It is believed that vascular accidents are caused by interrupted treatment. We had the opportunity of observing 2 cases of phlebitis of which one was obviously due to the treatment. Both occurred during interrupted treatments and were followed by small pulmonary infarcts.

However, during treatments administered with the recommended precautions, we never observed any untoward reactions. This seems to be due to regular supervision of the patients and to continuity of treatment. It is known that any neuroautonomic drug can, in certain cases, bring about unexpected reactions—reactions which are suppressed or decreased by prolonged, continuous action.

HYPOTHESES CONCERNING THE MODE OF ACTION

The mechanism of action of chlorpromazine is complex, probably multiple, and has given rise to hypotheses which are more or less contradictory or complementary. Starting with the laboratory investigations, they are as follows: First, we know that this drug constitutes the essential element of Laborit's "lytic cocktail" which has enabled him to bring about artificial hibernation by neuroautonomic disconnection.

Pocidalo, studying the result of excitation of the central extremity of the vagus nerve in the dog treated by chlorpromazine, speaks of "total chemical sympathectomy." To this can be compared the findings of A. Castaigne in experimental endocrinology wherein there is mentioned a "chemical hypophysectomy." Peruzzo has observed in vitro a decrease of oxygen metabolism especially marked in cerebral tissue. Particularly interesting are the studies of Dell and his co-workers, who have compared the effect of the drug with those obtained by Magoun, who studied the physiology of the reticulated substance of the mesodiencephalon with the electroencephalograph. Dell explains the action of chlorpromazine by its effect on sleep and by the decrease of the peripheral neuroautonomic tone. Decourt notes that sleep is not constant, and that it is impossible to obtain in the guinea pig, but that chlorpromazine produces a lethargy, which he calls "narcobiosis," even among the unicellular organisms.

In man, the various electroencephalographic studies seem to indicate that the drug, unlike the barbiturates, brings about a state of sleep which is hard to differentiate from physiologic sleep. It should be noted that most of the previous experiments study the action of the drug in the initial phase of sleep or somnolence, whereas this is perhaps not its most characteristic effect any more than is the thermic effect.

For this reason it may be useful to gather data which has been given us by clinical observation. The first thing to note is that patients are not put to sleep. We have seen that the psychic syndrome brought about by chlorpromazine is very special, that it is apparently characterized by a slowing down of perceptions, and by a weakening of these same perceptions as expressed by "lack of interest." Also, reactions in general are weak and delayed without any changes in the faculty of cognition. Emotional tone is at its lowest ebb. Furthermore, patients thus treated show a constant block of the orthostatic reflex as well as a series of indisputable neuroautonomic modifications. Thermic regulation is affected.

From the point of view of physiopathology, it should be noted that the psychiatric disorders most affected by this treatment are those which have been related to the pathology of the gray matter of the brain stem, such as disturbances in mood and changes in consciousness during waking hours. Chlorpromazine has also proved active in neurologic states related to mood and changes in the corpus striatum.

At present it is impossible to conclude with certainty the true mode of action of this drug. However, it does seem to have a neuroleptic action which exerts its effect mainly on the central and peripheral neuroautonomic system.

In a study of biologic reactions common to the different methods of shock treatment used in psychiatry, we have drawn particular attention to the principal processes involved in the alarm and defense reaction and its various forms described by Cannon, Hoff, Reilly, and Selye. This implicates a central mechanism and, in our opinion, it is at the diencephalohypophyseal level that the shocks, whether biologic or psychologic, exert their impact. It was logical therefore that we should investigate any therapeutic methods by which the nervous system, particularly the autonomic cerebral centers, could be brought to rest, and whether it was possible to interrupt the irritative or reactional process which may constitute the background of the mental disease, or even the disease itself.

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Chlorpromazine in Psychiatry*

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The following is a summary of our experience with chlorpromazine. This compound has been used for the past two years at the Psychiatric Hospital of Lyon, an institution of 2,200 beds for adults and children of both sexes suffering from various kinds of nervous disorders. More than 4,000 patients have been treated with chlorpromazine in the seven wards of this hospital.

Observations will be limited solely to psychiatric cases, since we have treated too few neurologic cases to draw any conclusions. After reviewing successively the evolution of this therapy, the different methods of administration of the drug, and the reactions it has produced, we shall consider its use in the different categories of patients treated in the hospital, and conclude with the impressions gained from the use of this treatment.

EVOLUTION OF CHLORPROMAZINE THERAPY

The use of chlorpromazine in psychiatry was inspired by the work of Laborit and his co-workers on artificial hibernation rather than by the work of the neurosurgeons. During the course of the first year, we used doses varying from 25 to 200 mg. per day. The compound was remarkably well tolerated; reactions and accidents due to orthostatic hypotension which we feared did not materialize. On the other hand, there were several attempts at suicide with very high doses (60 tablets of 25 mg.) resulting in a simple autohibernation which proved reversible without any complications.

The various states of agitation responded remarkably well to treatment. Considering the facts mentioned above, we decided to progressively increase the daily doses, particularly in cases of hebephreno-catatonia and paranoia. In these cases, we are currently using 600 mg. per day and sometimes up to 1 Gm. of chlorpromazine. Certain catatonics which had not been modified by the first doses were finally unblocked with doses of 600 to 800 mg. per day.

POSOLOGY

The 25 mg. tablet is the most currently used form of chlorpromazine. In most cases patient acceptance is excellent. We prescribe two to four tablets per day; for larger doses, a 100 mg. tablet is preferable.

The injectable form of chlorpromazine, contained in ampuls, is used in instances where patients refuse tablets and also in cases of emergency, for instance in the course of the manic episode. Both intramuscular and intravenous injections are used. In

* Translated from the French by Paul H. Pazery, Philadelphia, Pennsylvania.

cases of intense agitation which exhaust the patient and the people around him, we often administer, initially, a barbiturate of the type of sodium amytal to produce a so-called starter anesthesia which enables us to set up an intravenous drop by drop administration of chlorpromazine. We dilute 50 mg. of chlorpromazine in 250 cc. of isotonic solution to be absorbed in approximately two hours. This perfusion is repeated once or twice a day for three to five days after which intramuscular injections are substituted. But intramuscular injections, repeated three times a day, become painful after a while and cause indurations at the end of six to 15 days, according to the doses used and individual sensitivity. Treatment with tablets is then instituted and maintained for a long time, up to several months. Premature discontinuance of the treatment can bring about a recurrence of the disorders.

Certain patients prefer the compound in syrup form, in which instance the same doses are used. Chlorpromazine in suppository form is indicated in cases of gastric intolerance and when intramuscular injections become too painful. We abandoned the sublingual method of administration after a few trials. The doses it permitted were too small and it was often poorly accepted.

The management of patients on chlorpromazine differs widely from one individual to the other. Doses vary between two extremes: 25 mg. and 1 Gm. We frequently start with 100 mg., increasing this to 300 or 500 mg. on the fifth day. When the desired effect is obtained, we decrease the doses progressively, for instance by amounts of 50 mg. each week. The so-called inhibition syndrome varies considerably with individuals, certain patients must remain in bed with doses of 100 mg. while others can go to the department of occupational therapy even after doses of 800 mg.

REACTIONS

Chlorpromazine may give rise to reactions of the skin among nurses constantly in contact with the product, especially during the first year. These cases of eczematous contact dermatitis start on the hands and can affect the forearms, the neck, and the legs. The reactions which occur in subjects with a neuroarthritic heredity cannot be overcome by the usual methods of desensitization. They vanish completely and rapidly when the patient ceases to be in contact with the allergen. These reactions are becoming rare at the present time, as if a tolerance had developed among even the most sensitive nurses.

Among our patients, we have noted only a few rare cases (of sensitization); erythemas and eczemas have occurred in parts of the body which remain uncovered, probably due to a mechanism of photosensitization. In their original form, the tablets often caused burning sensations in the stomach; these are rarer now that the tablets are coated. Now and then we see sharper reactions—nausea and even vomiting—in which cases we make use of a different method of administration.

The orthostatic syncopes generally take the form of vertigo or sensations of inebriation and headaches; paradoxically enough it would seem that these reactions occur especially with the smaller doses of 50 to 100 mg. We are not considering the sinusoid tachycardias which occur frequently at the higher doses but which are well tolerated by the patients. In the same way certain Parkinson-like syndromes are

rarely indications for discontinuing treatment. They cease completely once the treatment is stopped. We have observed a few rare cases of hepatitis and edemas of Quincke which disappeared when the doses were reduced.

Chlorpromazine administered intramuscularly sometimes brings about high points in the temperature curve, and also phenomena of inflammation such as redness of the skin, induration, and pain which are always reversible. Thresholds of tolerance vary considerably with each individual. We also wish to point out the relatively good tolerance of the product which has practically no dangerous threshold.

RESULTS

States of excitation. States of excitation are the main indication for chlorpromazine. Complete control of psychomotor agitation is obtained by combining chlorpromazine intravenously and intramuscularly, eliminating the need for restraints, which are so hard on the patient.

The patient admitted in a state of frenzy, vociferating, and gesticulating, finds himself in a few hours in a state of complete calm and rest. He stays in bed, almost motionless, and without showing the frightening symptoms of a coma or a complete paralysis. He is overcome by a kind of somnolence accompanied by a beneficial lassitude of which he is perfectly conscious and which is rarely unpleasant to him. The physician can then make use of psychotherapy in his conversation which was initially rendered impossible by the flight of the patient's ideas.

Chlorpromazine acts remarkably well in all conditions of secondary excitation found in various psychotic and neurotic states, but it is also effective in states of manic agitation, so refractory until now to biologic therapy. Sometimes the episode seems literally nipped in the bud, other times it is merely slowed down and premature discontinuance of the drug would bring back the symptoms. It is generally necessary to use large doses to treat manic episodes. It can be said that out of 4,000 treatments given in our hospital, 1,500 were prescribed to overcome excitation states.

Chlorpromazine has greatly contributed to transforming the atmosphere of psychiatric hospital wards; it is an important factor in relaxation and return to normal.

Depressive states. The effect of this compound on depressive states is more controversial. In our experience at the Vinatier Hospital, chlorpromazine was effective in moderate cases of depression and anxiety. However, it cannot overcome serious cases of anxiety nor episodes of melancholia, where electroshock remains the treatment of choice.

Schizophrenia. Most of the schizophrenics at Vinatier hospital, about 1,000, have been treated with chlorpromazine. It has a remarkable effect on the catatonic and paranoid syndromes. We have already witnessed the literal "resurrection" of several dozen catatonics. In a few months, with average doses of 600 mg., we observed a progressive disappearance of inhibitions and a renewal of psychomotricity. But the effect is not permanent and the patient must continue treatment once he has left the hospital or the phenomena of blockage will reoccur and the inhibitions reappear.

In the paranoid forms, which account for approximately 30 per cent of the schizophrenics in the hospital, numerous instances of spectacular disappearance of delirium

have occurred. Autism, incoherent and delirious confusion, and symbolic disguises disappeared simultaneously. In certain patients, there seemed to be a constant relationship between the lessening of the morbid state and the quantity of drug absorbed. These fluctuations, probably related to variations in the mechanism of waking and sleeping, were reflected in the electroencephalograms. But in this group also we are obliged to continue medication or to reinstitute it periodically.

We prefer the Sakel* treatment in schizophrenias of the dementia praecox type.

Chronic states of delirium, paranoias. We treated approximately 500 paranoiac patients with chlorpromazine. Patients with well established deliriums are usually refractory to medication, particularly difficult were those with hallucinatory disturbances. Nevertheless, improvements in behavior are obtained, preventing episodes of agitation and anxiety. We had the satisfaction of controlling the disturbances of 3 severe paranoiac patients in our own department. These 3 patients had been placed in three separate buildings where they dominated the whole environment with their powerful personalities, multiplying conflicts, making life impossible for co-patients, and sabotaging all social therapy. They received intensive treatment with maximum doses and were kept apart for two months. This brought about an improvement in the interrelations between each building and promoted the creation of new traditions and a new atmosphere to which, afterwards, the 3 severe paranoiac patients had to adapt themselves.

Epilepsy. Generally speaking, chlorpromazine aggravates epileptic disturbances and increases the frequency of episodes. However, we have seen the disappearance, both clinical and electroencephalographic, of the signs of grand mal in one of our patients who was treated exclusively with chlorpromazine for two years with a daily dose of 100 mg.

Psychoses of short duration. The polymorphic delirious episodes or schizophrenic episodes are shortened, especially when agitation and incoherence of the delirious ideas dominate. We reserve opinion concerning episodes of primitive mental confusion for which we have frequently associated electroshock and chlorpromazine. We treated acute febrile delirium successfully by inducing a state of hibernation.

Alcoholism-toxicomanias (drug addiction). We found chlorpromazine to be a useful adjuvant medication in various forms of alcoholism which give rise to mental symptoms; we reserve it for those cases whose mental background presents a component of marked excitation.

We have no experience in the field of toxicomania as such cases have been extremely rare in the hospital.

Psychopathic personalities, behavior disorders. Chlorpromazine has been used at Vinatier on about 100 patients of this type. We have also used it at the psychiatric annex of the Lyon Prisons. These patients have a remarkable lability of mood and this medication is very beneficial during phases of agitation and aggressiveness, and episodes of depression and anxiety. The fundamental nature of the problem is unchanged but episodic treatment can avoid many conflicts and even untoward actions.

Senile dementia. In the same manner as many psychiatric hospitals, the Psychiatric

* Insulin shock therapy.

Hospital of Lyon is crowded with geriatric patients who are senile and for whom a better organized public health department could avoid institutionalization. The wards contained about 14 per cent of these senile patients. Chlorpromazine, administered to 300 of those who were agitated, especially at night, gave good results to all. However, the fundamental dementia remained unchanged.

Pediatric neuropsychiatry. States of agitation and impulsiveness come under the scope of chlorpromazine. However, it did not seem to us that it helped excited and distracted children to study in school in any way, even when it did prevent the flight of ideas. Doses used for children less than 8 years of age are 25 to 50 mg.; for children from 9 to 15 years of age we never administer above 150 mg.

REMARKS

In this short review, we have not covered all psychiatric fields. In particular, the experience we have had in this hospital does not include the large group of narcotics which make up the bulk of patients seen by the general practitioner. We have not considered the group of retarded and feebleminded persons who nevertheless make up about 18 per cent of the patients, but by taking into account their main symptoms we have included them in one of the categories previously mentioned. These patients were classified according to the state that predominated, whether it was a state of depression or excitation, a condition of delirium or disassociation, or epilepsy. We have not found that chlorpromazine had any effect on retardation itself. The drug seems to act in two fields, apparently distinct but in reality closely linked: the one is kinetic, the other nyctoemeral. Chlorpromazine acts on psychomotricity; it inhibits it in states of excitation and liberates it in states of inhibition. In catatonic and paranoid states it is both a therapy and a fascinating experiment at the same time. One has the impression, and this is confirmed by the electroencephalogram, that it modifies the threshold levels of sleep and waking. The paranoid deliriums, which it suppresses, are only colorful and luxuriant reflections of phases of sleep or degrees of hypnosis. Paranoids with fantastic deliriums and catatonics with desperately rigid attitudes, are "sleeping patients" that chlorpromazine "wakes up" or brings to a superior degree of lucidity. Yet the action of this drug in no way recalls the action of hypnogens or classical stimulants.

These few figures give some idea of the quantity of chlorpromazine used during the last two years in the hospital.

	1953	1954
Ampuls of 5 cc. at 25 mg.	17,400	65,278
Ampuls of 2 cc. at 50 mg. (i.v. inj.)	9,000	7,732
Tablets, 25 mg.	132,000	791,867
Suppositories, 100 mg.	0	23,250
Drops, bottles 10 cc.	0	2,300

We began to use suppositories in April, 1954 and chlorpromazine in drops, November 5, 1954.

CONCLUSIONS

Chlorpromazine is a new advance in the progress of therapeutics, a milestone just as important as electroshock was about 10 years ago. Two years of intensive experience have led us to increase considerably the range of dosage and shown how well the drug is tolerated. Its indications seem to be getting more defined. Chlorpromazine acts remarkably well on psychomotor agitation, whether it be a component of a syndrome or whether it is in itself an entity, by which we mean manic episodes and, to a certain extent, anxious melancholias, and in cases where the waking state is partly disturbed, particularly in catatonics and paranoids.

The results of this therapy are also being felt in the psychiatric ward considered as an aggregate. As it reduces both individual and collective agitation and aggressiveness, it contributes to the improvement of the ward atmosphere. Occupational therapy and all social therapies can be increased to the great advantage of all the patients and also for the greater benefit of the nurses and personnel.

SUMMARY

Within the confines of a psychiatric hospital of 2,200 beds, 4,000 patients had been treated with chlorpromazine for the last two years. With use, posology has been increased to doses ranging up to 1 Gm. per day, often necessary in manic episodes and in catatonic patients. The compound is remarkably well tolerated and reactions are minimal.

The advent of chlorpromazine is of considerable value in states of excitation of varied etiology and supersedes the usual methods of sedation. It is also helpful in moderate cases of anxiety. Lastly, in the field of schizophrenia, it brings about spectacular pacification in paranoiac and catatonic states. It has little effect on serious depressive cases and no influence in states of mental deficiency or deterioration. Its inhibitory effect on psychomotricity is perhaps due to its general action on metabolism. It would also seem to be effective on catatonic phenomena and paranoid thought disturbances by modifying the thresholds of sleeping and waking.

Chlorpromazine has greatly helped to bring about an atmosphere of peace and quiet in the wards of this Psychiatric Hospital and has enabled physicians to increase the use of occupational therapy in their attempts to return patients to a normal life.

Use of Chlorpromazine in the Management of Acute and Postalcoholic States

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Therapeutic measures currently employed in the management of individuals who over-indulge in alcohol are directed to hasten the oxidation of alcohol, correct nutritional deficiencies, and relieve the patient of the manifestations of cerebral disorganization. For the latter purpose a wide variety of sedatives has been employed. The principal objection to their use has been that they tend to be either ineffective or produce additional central nervous system depression and confusion. In some instances habituation and even addiction may result.

This discussion is based on experiences with chlorpromazine in the management of over 500 patients with disturbances resulting from the ingestion of alcohol. Accurate evaluation of the efficacy of chlorpromazine in the management of acute and postalcoholic states is best accomplished by grouping the subjects according to the classification of Victor and Adams.[1] Group I includes those subjects with acute inebriation, group II those in whom signs and symptoms usually occur after the cessation of any alcoholic debauch and are manifested by tremor with or without transitory halucinations, and group III comprises those subjects with typical delirium tremens.

GROUP I: ACUTE INEBRIATION

Subjects comprising this group are seen most frequently in the emergency room; occasionally, however, the physician may be called to the home. Hospitalization is rarely necessary when a reliable individual is available to help with care. Medical attention is usually sought when the patient becomes disturbed, combative, or when nausea and vomiting seem excessive. The concentration of alcohol in the blood of such patients may vary considerably, from 100 to 250 mg. per cent.

The administration orally (or intramuscularly, if necessary) of 50 mg. of chlorpromazine produces within 30 to 45 minutes a somnolent state from which the patient may be easily aroused. If spontaneous awakening occurs, nutritious fluids should be given by mouth and the same dose of chlorpromazine repeated. Additional doses may be given if it is necessary to induce sleep for at least 12 hours, to insure complete oxidation of the alcohol and to obviate the desire to alleviate withdrawal symptoms by resumption of drinking. Doses of chlorpromazine greater than 50 mg. are usually not necessary, but may be given without fear of producing marked central nervous system depression even when the concentration of alcohol in the blood is high. The salutory influence of chlorpromazine upon the acute alcoholic state is of considerable interest. It has been observed that the drug neither influences the

rate of disappearance of alcohol from the blood nor augments the effect of alcohol by producing sufficient central nervous system depression to demonstrably reduce the cerebral metabolic rate.[2] Clinically also there has been no unequivocal demonstration of either an additive or true synergism between these two depressants. It would appear that chlorpromazine tends to induce a fairly specific inhibition of subcortical areas while the commonly encountered blood concentrations of alcohol involve functionally higher portions of the cerebrum. The latter under usual circumstances undoubtedly subject to afferent stimuli from lower brain areas may be shielded by "blocking" the effect of chlorpromazine so that the clinical state may simulate that of an augmented depression.

GROUP II: POSTALCOHOLIC TREMULOUSNESS

The majority of patients admitted to the alcoholic wards fall into group II. The clinical features of this group have been so admirably described by Victor and Adams[1] that we have taken the liberty of quoting freely from their paper:

"The prototype of this group is the spree or periodic drinker. After several days he becomes tremulous most particularly after the relative abstinence that occurs during sleep. His tremulousness in the morning is so pronounced that he seeks to quiet his nerves by a few drinks. When first seen in the hospital he is alert, jumpy, and startles easily. His face is flushed, conjunctiva injected, and there is usually mild tachycardia. Anorexia is universal; nausea and retching are common. He may complain of insomnia and craves rest and sleep. Tremor is the outstanding feature of this illness. Over a period of a few days the tremor, flushed facies, and anorexia subside. However, the over-alertness, the tendency to startle easily, the jerkiness of movement may persist for a week. The curious inner shakiness and uneasiness may not leave the patient completely for 10 to 14 days and only at the end of this time is the patient able to sleep undisturbed through the entire night without sedation. Symptoms of disordered sense perception form an interesting and disturbing feature in one quarter of these patients. The hallucinations may be visual, auditory, a mixture of the two, or very rarely tactile or olfactory."

The routine presently employed in the majority of these subjects is as follows: on admission 100 mg. of chlorpromazine are administered intramuscularly. Blood pressure is recorded in all subjects before, and 30 to 60 minutes after the initial dose of the drug. All but a very few of these subjects fall asleep for three to eight hours. The onset of sleep is usually from 30 to 45 minutes after intramuscular injection and from 45 to 60 minutes after oral therapy. When the patients show evidence of spontaneous awakening, fluids (water or fruit juices) are offered and if refused administered parenterally. In order to evaluate the efficacy of chlorpromazine alone additional supportive therapy in the majority of patients has been withheld whenever possible. The frequency of further administration of chlorpromazine is determined by the clinical response of the patients and it may be necessary to repeat the initial dose as often as every three hours. In less severely disturbed patients subsequent doses may be decreased to 50 mg.

The somnolent state induced by chlorpromazine is light. Subjects can be readily

aroused by slight stimulation and often by extraneous noises. Those subjects not actively hallucinating are rational and cooperative when aroused and upon cessation of stimulation promptly return to their somnolent state. Deep sedation and confusion attendant upon the use of other sedatives have not been encountered, even when large doses of chlorpromazine were administered.

The control of motor excitement manifested by tremulousness is usually achieved following administraton of the drug. Tremulousness returns if chlorpromazine is discontinued prematurely but can be brought under control again upon resumption of therapy. The reduction of involuntary motor activity without producing deep sedation is one of the most dramatic effects of the drug.

In the early stage of treatment chlorpromazine controls tension by the induction of sleep. However, subjective disturbances seem to be less readily controlled than motor manifestations and on awakening, the patients often complain of "nervousness inside," though appearing outwardly calm. Many of these patients request the type of medication they have received on previous admissions, although some volunteer that they prefer the present therapy. These latter patients may well represent those experiencing less intense subjective disturbance. After recovering from the acute phase all patients are transferred from the admitting to convalescent wards. Chlorpromazine is usually continued while in the latter areas and during this time the tranquilizing effects of chlorpromazine on subjective reactions are still beneficial.

Although subjects with transitory hallucinations usually become somnolent following administration of the drug, the hallucinations are not directly suppressed but subside gradually over a course of one to several days. Failure of direct control of hallucinosis by chlorpromazine is further indicated by the observation that five subjects while being treated for acute tremulousness developed typical delirium tremens.

The acceptance of oral fluids obviated the necessity for parenteral therapy in the majority of cases. Even those subjects admitted with anorexia and vomiting may request and be able to retain food and fluids within 24 hours after the administration of chlorpromazine is begun.

The recovery time of subjects varies from two to five days, depending on the severity of the disturbance. In many instances, hospitalization has been continued for longer periods only because of the legal nature of their commitment. It would seem from the data presently available that the hospital stay is otherwise appreciably reduced by the use of chlorpromazine.

The over-all therapeutic value of chlorpromazine in this group of patients is unquestionable. Probably of equal importance from the point of view of hospital administration is the influence of the drug on ward problems. In our experience the incidence of assault and the necessity for restraint or "seclusion" since the introduction of chlorpromazine has been minimal. The workload of attendants, nurses, and physicians has been reduced. The "decibel level" of the alcoholic ward is now one of the lowest in the hospital. Although accurate cost analysis figures are not available it would seem they should be decreased since oral feeding has largely supplanted parenteral nutrition and the use of massive vitamin therapy, relaxants, and sedatives has been considerably reduced.

GROUP III: DELIRIUM TREMENS

Delirium tremens represents the most serious clinical complication resulting from alcohol ingestion. It is characterized by excessive and almost continuous motor activity, extreme lability of the autonomic nervous system, and marked disturbances in sensual perception. Its course is variable; in the majority of cases the delirium ends abruptly within 72 hours, less frequently it may subside gradually, and rarely there may be a recurrence after a lucid period. Mortality is high, approximately 15 per cent succumbing from the disturbance or associated disorders.

Reports[3, 4] concerning the use of chlorpromazine in the treatment of delirium tremens indicate that its many properties contribute toward inducing a favorable response (tranquilizing, autonomic blockade, hypothermic, antiemetic, anticonvulsant). Unfortunately, some of the cases presented in these reports were classified as subacute delirium tremens, and in many instances a multiplicity of drugs was given along with chlorpromazine.

We have used chlorpromazine for the management of 75 cases with full-blown delirium tremens. The routine adopted is similar to that described for subjects with acute tremulousness (group II). Intravenous administration of chlorpromazine has not been found to offer any advantages over the intramuscular route. Fluids are given intravenously when oral administration is not feasible or when dehydration seems excessive. Agents other than chlorpromazine have been deliberately withheld.

In the majority of patients chlorpromazine seems to diminish motor activity, induce sleep, and lessen the frequency of hallucinations. The effectiveness of the drug seems to depend upon repeated rather than massive doses; often no apparent clinical change may be noted after the first or even the second injection, and in several subjects the intravenous administration of 200 to 300 mg. within a period of 30 minutes failed to appreciably influence the delirious state.

It is our impression that the duration of the delirium is not influenced by chlorpromazine. Recovery time varies from two to six days, a finding not significantly different from that for other therapeutic regimens. We have previously mentioned that several of our subjects developed delirium tremens while receiving chlorpromazine for acute tremulousness. Six subjects who apparently had recovered from an attack of delirium tremens had a recurrence even though they were still receiving chlorpromazine.

There have been 8 deaths in our patients, 4 due to vascular collapse, 1 to hyperthermia, and 3 to undetermined causes. The number of deaths approximates the mortality figures reported by others for treating this type of patient with the measures commonly employed.

Our experience to date regarding the use of chlorpromazine in subjects with delirium tremens suggests that it may ameliorate, to some extent, the manifestations in those subjects undergoing spontaneous improvement. It is apparently without effect on the duration of illness. Nevertheless, it is our opinion that chlorpromazine possesses definite advantages over the sedatives previously employed and that its many actions are for the most part desirable and valuable in the management of delirium tremens. In view of the potentiating action of chlorpromazine and other

sedatives such combinations may prove to be more effective than chlorpromazine alone in the management of delirium tremens. This would obviate the need for large doses of the sedatives which act primarily as cortical depressants. We have given 6 subjects in delirium tremens intravenous alcohol along with chlorpromazine and do not feel that this combination has any particular value.

COMPLICATION FROM THE USE OF CHLORPROMAZINE

It is not the purpose of this paper to review all the side effects of chlorpromazine. It is pertinent, however, to mention those found to be particularly troublesome. In addition, a brief discussion of the influence of chlorpromazine on the complications most frequently encountered in subjects with chronic alcoholism would seem to be warranted.

HYPOTENSION

Hypotension following chlorpromazine administration has been by far the most troublesome complication. In the majority of subjects there is a slight and inconsequential reduction in pressure and a compensatory tachycardia. Occasionally orthostatic hypotension has occurred; most subjects, however, are content to remain in bed. Chlorpromazine is now being used on all services of the hospital and probably well over 1,000 patients have received the drug for various indications. The drug has been administered orally, intramuscularly, and intravenously in doses varying from 25 to 300 mg. Marked hypotension has occurred in 11 cases. The hypotensive action is not dependent on the dose since in 3 of the patients it was noted after the administration of only 25 mg.

In our experience vascular collapse due to chlorpromazine most frequently occurs following the initial injection of the drug and is seldom first manifested upon subsequent administration. It is important when chlorpromazine is given for the first time that blood pressure is recorded before, and at 30 and 60 minutes after the administration of the drug to determine if the patient is a hypotensive-reactor.

The hypotension resulting from chlorpromazine is readily reversed if recognized early. In only one subject with delirium tremens was it probable that the vascular collapse could be primarily attributed to chlorpromazine. In this case hypotension was not detected until six hours after the initial dose of chlorpromazine. Intensive therapy restored pressure to normal values and the patient subsequently recovered from his delirium, only to succumb several days later from acute renal insufficiency. One can not be certain that the autonomic instability associated with delirium tremens may not have sensitized the patient to the hypotensive action of chlorpromazine. Several recent publications,[5, 6] however, indicate that chlorpromazine possesses "antishock" activity by virtue of its adrenolytic properties.

INFLUENCE OF CHLORPROMAZINE ON COMPLICATIONS FREQUENTLY ENCOUNTERED IN ALCOHOLISM

Anorexia and vomiting. The antiemetic and hypnotic properties of chlorpromazine are particularly valuable in the control of the gastrointestinal disturbances fre-

quently noted in alcoholic subjects. There can be no doubt that rapid correction of dehydration and nutritional deficiencies contribute to the recovery of such patients. In the past this has been accomplished with great difficulty, because of the disturbed state of the subjects and the inadequacies of parenteral therapy. There is no evidence that chlorpromazine directly stimulates the appetite although it may well produce this result indirectly because of its antiemetic and tranquilizing properties.

Liver damage. There have been several reports,[7, 8] describing the development of jaundice following prolonged use of chlorpromazine. The question naturally arises as to whether the use of chlorpromazine will aggravate existing liver disease in a population known to have a high incidence of such disorders. In over 500 alcoholic subjects treated to date we have not seen a single case of jaundice resulting from chlorpromazine administration. We have not hesitated to use the drug in cases with hepatic enlargement because it was felt that the improved nutrition regularly resulting from its use far outweighed any possible aggravation of liver damage. Furthermore, the development of jaundice has not been reported in the course of short periods such as those used in the treatment of patients presently under consideration.

Alcoholic epilepsy. One might expect from animal studies that chlorpromazine would decrease the incidence of seizures because of its effect in raising the threshold of excitability to certain drugs.[9] Unfortunately, accurate statistics are not available on the influence of chlorpromazine on the incidence of "rum fits." Seizures have occurred in a number of group II subjects even while on relatively large doses of chlorpromazine. It is felt, however, that in those subjects postconvulsive excitement was abolished.

Head injuries. The high incidence of head injuries in the alcoholic population is generally recognized. These patients must be carefully observed for signs of increased central nervous system depression. The drugs presently available usually depress the central nervous system and may thus mask evidence of brain pathology or, even worse, reduce the activity of the vital centers to a dangerous level.

We have administered chlorpromazine (50 mg. four times a day) to 6 patients with skull injuries with gratifying results. The patients became quite comfortable, and restlessness and motor activity were considerably reduced; there was no depression in the state of consciousness, respiration was not affected and analgesics, when required, were effective in relatively small amounts.

SUMMARY AND CONCLUSION

Chlorpromazine has been used for the management of subjects acutely inebriated, with alcoholic tremulousness, and with delirium tremens. Relatively small doses were extremely effective in inducing somnolence in the combative or disturbed acute alcoholic subject. The management of subjects with acute alcoholic tremulousness was greatly enhanced by the use of chlorpromazine because of its tranquilizing and antiemetic properties. In the majority of subjects with delirium tremens chlorpromazine seemed to alleviate, to some extent, the manifestations of the condition but not its duration. The effectiveness of the drug was not as pronounced as in the other two alcoholic states. Hypotension was the most serious complication of chlor-

promazine administration but, if detected early, is readily reversible. Management of the complications frequently encountered in the alcoholic population (gastrointestinal disturbances, nutritional deficiencies, liver damage, alcoholic epilepsy, and head injuries) are reduced by chlorpromazine administration.

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Uses of Chlorpromazine in Anesthesia and Surgery

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Since the introduction of curare into anesthesia, about 10 years ago, few drugs have received so much attention or aroused so much interest from surgeons and anesthetists as chlorpromazine. Similarly the concept of controlled inhibition of the autonomic nervous system or "artificial hibernation" is only equalled by that of muscular relaxation without deep anesthesia in its deviation from orthodox teaching. Chlorpromazine was introduced into the English speaking countries as recently as 1953 and its general use in many centers is of even more recent origin. Consequently, it is too early to decide what part it will eventually play in anesthesia and in surgery. This paper briefly reviews some of the uses to which it has been already put and discusses the hazards associated with its administration.

Chlorpromazine is a drug to which many properties have been ascribed and it has recently been suggested that its main action is depression of hypothalmic and medullary centers with specialized autonomic activity.[9] If used for only one of its actions it is inevitable that undesirable side effects may sometimes result from the action of chlorpromazine on other structures. This applies particularly to its vasodilating properties. A variable degree of postural hypotension invariably follows the use of chlorpromazine, usually accompanied by a compensatory tachycardia. Sedation also occurs regardless of the use for which chlorpromazine has been given.

"Autonomic blockade" is a vague term which is sometimes used to describe the antiadrenaline action, vasodilating, and other similar properties of chlorpromazine. This is probably the basis for its use in artificial hibernation. Since the latter has been discussed in detail in a recent issue of this journal, references will only be made to some of the other clinical applications of these properties. The author has described the use of chlorpromazine as premedication before the operative removal of pheochromocytoma[3] and its intravenous use to prevent hypertensive attacks during the handling of the tumor.[4] The beneficial effects in this condition will depend largely on the amount of norepinephrine excreted by the tumor, for while chlorpromazine has a very powerful anti-epinephrine action, it only slightly diminishes the effects of norepinephrine.[5]

Postural ischemia can be obtained during anesthesia by the judicious use of chlorpromazine. It is not as intense as with hexamethonium, and as seen in figure 1, can be overcome by direct stimulation of the base of the brain. Coughing or straining will also temporarily counteract the hypotension, which can be easily revered by norepinephrine. Patients who have had chlorpromazine are particularly susceptible to blood loss, which will cause a more marked fall in blood pressure than in normal

* Its use does not exclude the necessity for administering benzodioxone and Roegitine, but the requirements of these are much reduced and their action more prolonged.

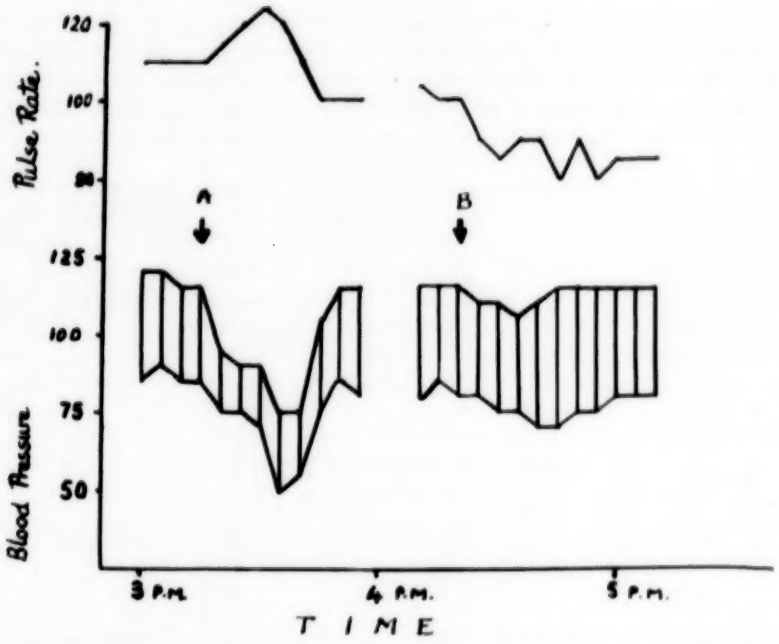

FIG. 1. Effect of 25 mg. chlorpromazine given intravenously. A. In a patient who had lost about 300 ml. blood. This was rapidly replaced and blood pressure returned to normal. B. Same patient with blood loss completely replaced.

persons (figure 2). Chlorpromazine also makes patients very sensitive to the hypotensive action of hexamethonium and Arfonad, which should be administered in greatly reduced dosages.

The peripheral vasodilatation produced by chlorpromazine has been used in the conservative treatment of peripheral vascular disease.[2] Results indicate that it is of value in acute and chronic vasospastic disease and early vascular occlusion. In frostbite the oral administration of 100 mg. of chlorpromazine daily in divided doses, gives as good results as repeated sympathetic blocks and at the same time produces useful sedation. Part of the action of chlorpromazine as an adjuvant to the production of hypothermia by surface cooling is due to its vasodilating action. This will be discussed more fully later.

Sedation with chlorpromazine resembles normal sleep in many respects. Patients can be easily awakened to answer questions, and yet drop off to sleep again once they are left undisturbed. The deep narcosis which follows the use of barbiturates is not seen. Of even greater importance is the mental effect of the drug which is observed with subnarcotic doses. This effect is characterized by a loss of apprehension and awareness of the surroundings. For this reason chlorpromazine is an extremely good sedative for administration on the night before an operation. Where

possible it should be given by mouth in doses of 100 to 150 mg., or in half this dosage combined with a small amount of barbiturate. For afternoon operations an additional 50 mg. can be given early on the morning of the operation. For routine premedication the drug should be given parenterally in 50 mg. doses with meperidine and/or phenergan. Thus administered it will produce a quiet, relaxed patient with

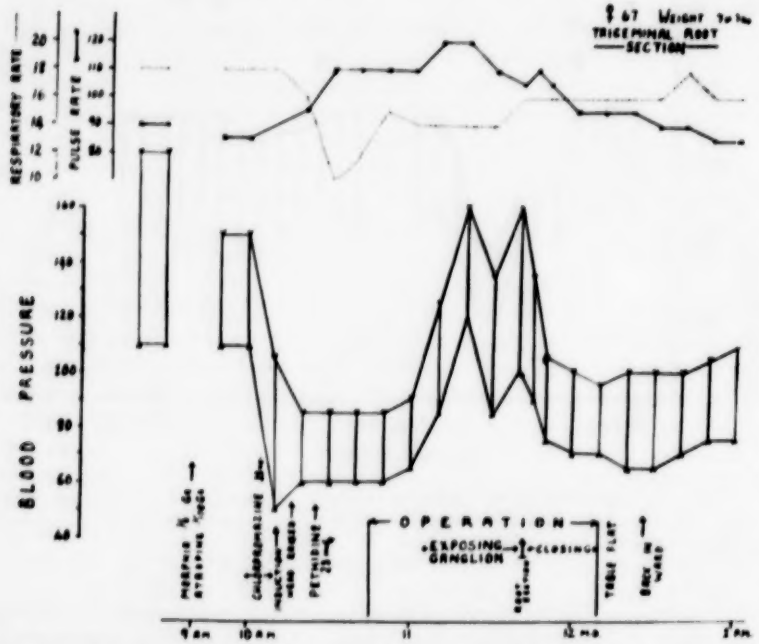

FIG. 2. Postural hypotension following the use of chlorpromazine in the operation for trigeminal root ganglion section. Patient was lying in 10 degree head-up tilt during the administration of the chlorpromazine and induction of anesthesia which was with thiopental 200 mg., topical application of xylocaine to the larynx, and then tracheal intubation. Anesthesia was continued with nitrous oxide-oxygen and trilene. Blood pressure returned to normal about four hours after return to ward.

very little respiratory depression; the amount of anesthetic or relaxant subsequently required will be greatly reduced. Even when the use of chlorpromazine has been limited to sedation the night before operation, a diminution in anesthetic requirements can still be detected for 24 hours. Endotracheal intubation is facilitated and incidents of vagal origin are minimized. Apart from any antiemetic action which chlorpromazine possesses of its own, the fact that opiates are not given remarkably reduces the amount of postoperative vomiting.

The syngeristic effects of chlorpromazine with narcotics and analgesics are also seen in the diminution requirements of analgesics after operation. However, its routine postoperative use is not recommended because the prolonged immobility may increase the incidence of respiratory complication and thrombosis.

A word of warning concerning the dosage and methods of administration of chlorpromazine is necessary at this stage.* Subcutaneous injections should not be given, and when the intramuscular route is used the injection should be deep into the muscle. The incidence of untoward sequelae can be reduced and the onset of action hastened by combining the drug with hyaluronidase. When the intravenous route is adopted the drug should be diluted to a strength not exceeding 50 mg. in 20 ml. Thrombophlebitis may result from the use of more concentrated solutions. The degree of hypotension and tachycardia is more marked with rapid injection and the drug should either be given slowly in a drip, or if given by the intermittent method, the rate should not exceed 10 mg. in five minutes, especially in elderly and debilitated patients. The collapsed appearance which is sometimes seen after the administration of chlorpromazine (and is due to vasodilatation) may suggest the use of drugs such as coramine. The author has heard of severe collapse and even sudden death when coramine was given to persons who had received chlorpromazine. He has also observed the depressant effect of this combination on the isolated heart-lung preparation. Posture, oxygen, and occasionally norepinephrine are the recommended lines of treatment for collapse after an overdose of chlorpromazine.

Theoretically, chlorpromazine will inhibit vomiting due to drugs which act on a chemoreceptor area in the floor of the fourth ventricle. In clinical practice it has proved valuable in controlling emesis from a large variety of causes, and is one of the most useful antiemetic drugs known. Among the many causes of vomiting which have been successfully treated with chlorpromazine are hyperemesis gravidarum, postradiation, and postoperative vomiting, and that due to drugs and malignant disease. The initial dose must be given parenterally until the emesis is controlled, after which oral medication will suffice. It has been stressed that before chlorpromazine is used the cause of the nausea and vomiting should be reasonably well established, otherwise a more serious clinical condition may be obscured by the wide range of usefulness of the drug.[7]

In the doses used as premedication or for artificial hibernation, chlorpromazine itself does not cause an appreciable degree of hypothermia. However, by its vasodilating action and its ability to inhibit shivering,[8] it is a valuable adjuvant in the production of hypothermia by surface cooling.[4, 10] The best results are obtained when the patients are premedicated with chlorpromazine, lightly anesthetized, and enclosed in a cooling blanket or covered with ice bags. If shivering occurs or peripheral vasoconstriction appears (as judged by the sharp fall in skin temperature), more chlorpromazine should be given. In an unpublished series of about 50 cases using this technique the author found that a rectal temperature of about 30 C. should be reached in 90 minutes in adults. A typical case is shown in figure 3. For cardiac surgery the temperature should be allowed to drop to about 24 C., but for neurosurgical procedures 28 to 30 C. will suffice. Chlorpromazine has also been used for the induction of therapeutic hypothermia in head injuries, postoperative pyrexia,

* Patients vary enormously in response to this drug, and especially after its intravenous use. It is always desirable to give an initial 10 mg. dose and, depending on the effects of this on blood pressure, pulse rate, and depth of consciousness, subsequent requirements can be judged.

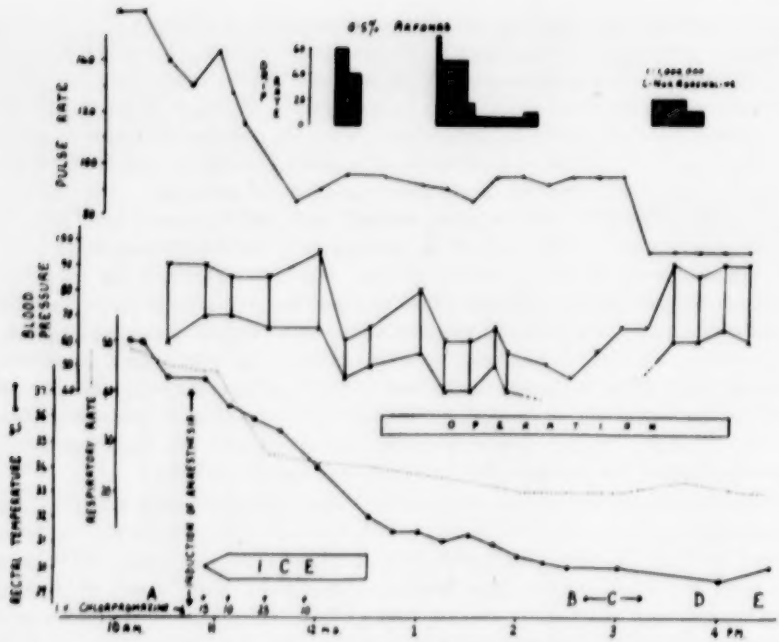

FIG. 3. Use of chlorpromazine for the induction of hypothermia by surface cooling. Operation was for excision of cerebral aneurysm. The patient was a 40 year old woman, premedication was with chlorpromazine 50 mg. and hyoscine 1/150 Gr. (0.42 mg.). Anesthesia was induced with 100 mg. thiopentone and 20 mg. suxamethonium. An armoured endotracheal tube was passed, the pharynx packed with moist gauze, and the anesthesia was continued with nitrous oxide-oxygen by a T-piece technique. The aneurysm was excised at B, a pint of blood given at C, the dura closed at D, the patient returned to the ward at E. (Reproduced by permission of the British Journal of Anaesthesia (1955) 27, 93, from paper by C. B. Sedzimir, D. Jacobs, and J. W. Dundee.)

edema of the brain, and thyrotoxic crises. While most of the benefit is due to a reduced oxygen consumption, it is possible that an attenuation of the response to stress plays some part.[6]

In psychiatric practice chlorpromazine has a wide range of usefulness. This is based on two properties already mentioned above, sedation and relief of anxiety or "pharmacologic lobectomy." The latter is particularly valuable in patients suffering from inoperable tumors, and the routine use of 50 to 200 mg. of chlorpromazine daily in divided doses is strongly recommended where patients have a marked insight into the cause of their malady. An additional factor is that chlorpromazine markedly enhances the action of analgesics. Doses which have become ineffective can, with the addition of chlorpromazine, once more give good relief of pain. The author has been particularly impressed by the combination of 1.5 mg. levorphan (Dromoran) and 25 to 50 mg. chlorpromazine given three to six times daily as required. This is discussed more fully elsewhere.

Other suggested uses of chlorpromazine which have not been fully established include symptomatic relief from duodenal ulcers and the dumping syndrome. This is based on its inhibitory effect on gastric secretions and spasmolytic action on the intestine.[1] It has also been recommended in status asthmaticus, "neuroticosis" in children, fevers, and carbon monoxide poisoning.

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The Value of Chlorpromazine in the Management of Pain

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Although intensive research has advanced present knowledge of pain considerably, the subject has remained enigmatic in more respects than one. For instance, numerous contradictory reports are available in the literature on the measurement of pain threshold alone. This is significant in a negative way. An absolutely satisfactory method for measuring pain threshold still has to be found. Along the same lines, although so many drugs are offered for pain relief, the ideal analgesic is not yet available. Perhaps a fresh approach is needed. Chlorpromazine, with its ability to augment and prolong the action of most central nervous system depressants might supply an answer to the perplexing problem of pain relief.

There are various ways of evaluating the efficacy of an analgesic drug. The human subject is ideal for this purpose because pain studies in animals are so limited in their applicability to humans. The reason perhaps is the fact that even if pain perception is a physiologic phenomenon with well established anatomic pathways, it is so intimately associated with pain reaction and all its emotional overtones. It is obvious that animal and human reactions to pain differ considerably. Moreover, reactions even vary in the same animals and in the same human beings on testing on various occasions. The effectiveness of an analgesic drug may thus be studied in normal human subjects by providing a pain stimulus, or in subjects suffering from pain. The latter method, readily available and convenient, was used in these series.

Objectivity is desirable in any experimental study. However, since pain perception may be divorced from pain reaction only with considerable difficulty, a subjective element will always creep into the picture when pain relief is studied. At best, therefore, conclusions derived from studies such as these, being fraught with presently insoluble complexities, are quite guarded.

A previous study of a group of pain patients[1] has shown encouraging results. A restatement and analysis of the data obtained in this study may contribute to a more effective assessment of the value of chlorpromazine in pain.

Several points stand out in this study. Table I, which gives a summary of the 18 cases treated, shows that 16 benefited from the administration of chlorpromazine by diminishing the amount of narcotic necessary to produce pain relief. The degree of relief was good in 13 cases and fair in 3 cases; 2 cases showed no relief. Reduction in the amount of narcotic needed to give analgesia after chlorpromazine was:

No. of cases	Narcotic dose reduced by
6	20–30 per cent
5	50 per cent
2	60–66 per cent
3	75 per cent
2	None

In 2 of the cases, it was possible to change from a stronger to a weaker narcotic, that is, from morphine and dromoran to codeine and demerol. The change to codeine in one of these cases was not too significant in view of the fact that the amount

TABLE I

Effects of Chlorpromazine on Narcotic Requirements

Site of lesion Colon and rectum	Initial narcotic		Chlorpromazine 24 hrs.	Narcotic after chlorpromazine per 24 hrs.		
	Kind	Dose/24 hrs.		Kind	Dose	Relief
Case 1	Dromoran	80 mg.	100–200 mg. (O)*	Dromoran	40 mg.	
				Morphine	80 mg.	Good
Case 2	Dromoran	20 mg.	100 mg. (IM)	Codeine	360 mg.	Good
Case 3	Dromoran	40 mg.	125 mg. (O)	Dromoran	10 mg.	
				Morphine	64 mg.	Good
Case 4	Dromoran	120 mg.	125–400 mg. (O)	Dromoran	60 mg.	Good
Case 5	Dromoran	80 mg.	50–400 mg. (O)	Dromoran	18–32 mg.	Good
Case 6	Dromoran	60 mg.	150–200 mg. (O)	Dromoran	15 mg.	Good
Tongue and mouth						
Case 1	Codeine	360 mg.	200 mg. (O)*	Codeine	240 mg. (O)*	Fair
Case 2	Codeine	360 mg.	100 mg. (O)	Codeine	120 mg. (SC.)	Fair
Case 3	Dromoran	30 mg.	150 mg. (IM)	Dromoran	20 mg. (SC.)	Good
Case 4	Codeine	360 mg.	50–75 mg. (O)	Codeine	180 mg. (SC.)	Good
Case 5	Dromoran	120 mg.	200–400 mg. (O)	Dromoran	30–80 mg. (SC.)	Good
Gastric ca.	Dromoran	60 mg.	200 mg. (IM)*	Demerol	400 mg. (SC.)*	Good
Larynx	Dromoran	30 mg.	50 mg. (O)	Dromoran	15 mg. (SC.)	Good
Bronchus	Pantopon	160 mg.	75–150 mg. (O)	Pantopon	120 mg. (SC.)	Good
Adrenal	Dromoran	40 mg.	75–200 mg. (O)	Dromoran	15–30 mg. (SC.)	Good
Pancreas (carcinoma)	Morphine	180 mg.	125–300 mg. (O)	Morphine	60–90 mg. (SC.)	Fair
Pancreatitis	Dromoran	30 mg.	400 mg. (O)	Dromoran	30 mg. (SC.)	None
Testes	Codeine	720 mg.	75 mg. (O)	Codeine	180 mg. (SC.)	
				Demerol	600 mg. (SC.)	Poor

* O = orally; IM = intramuscular; SC. = subcutaneous.

of codeine necessary to provide relief was almost equal in potency to the dromoran previously used. See the following table II on the comparative potency of analgesic drugs employed.

Table III illustrates the average 24 hour dose of chlorpromazine utilized in this series and the concommitant reduction in narcotic dosage in per cent.

It appears as though the optimum oral dosage or intramuscular injection is around 100 to 200 mg. in 24 hours. A case of pancreatitis where 400 mg. in 24 hours was administered showed no relief at all; however, the significance of this observation is obscure.

Certain incidental observations on this group of patients appear significant. Sev-

TABLE II

Comparative Potency of Narcotics Employed

Narcotic	Dose	Potency
Morphine*	15 mg.	1
Dromoran	5 mg.	3
Demerol	100 mg.	1/7
Codeine	60 mg.	1/4
Pantopon	20 mg.	1/3

* Morphine taken as 1 in potency.

eral patients who were bedridden became ambulatory to a limited extent, others developed a detached attitude towards their pain. In those individuals in whom the narcotic dose was only slightly reduced, this detached attitude developed after chlorpromazine seemed to mitigate their condition considerably.

In another series[1] utilizing ambulatory clinic patients, doses of chlorpromazine varied from 25 to 50 mg., either orally or intramuscularly. Significant relief was observed in 9 out of the 12 patients seen. One patient was completely relieved by chlorpromazine and no further narcotics were necessary. Being outpatients, no rigid control could be exercised over these cases.

DISCUSSION

The question that arises is whether or not chlorpromazine has analgesic properties. It is difficult to answer this query categorically. Patients in this study when questioned maintained that their pain was still present and of the same intensity, and yet did not seem to bother them. How can such seemingly contradictory conditions exist side by side? Assuming that the intensity of pain remains the same, the

TABLE III

Average Dose of Chlorpromazine and the Reduction in Narcotic Dose

Dose of chlorpromazine in 24 hours	No. of cases	Reduction in narcotic dosage
Less than 100 mg.	3 (2 / 1)	50% / None
100–200 mg.	10	20–75%
Greater than 200 mg.	5 (4 / 1)	33–66% / None

chlorpromazine added to the narcotic the patient is taking contributes to the impairment of the patient's ability to interpret his pain. Still, it must be admitted there is no proof showing that chlorpromazine may not influence the perception of pain. On the other hand, no proof to the contrary is available. To state unequivocally that chlorpromazine is an analgesic by virtue of its ability to interfere with the

interpretation of pain would be begging the question. Furthermore, an individual whose ability to interpret has been modified somewhat is an unreliable judge of his own condition.

How then does chlorpromazine exert its effect? Does it supply or augment the euphoric state caused by a narcotic analgesic so that it brings about a dissociation of the individual's reaction to and his perception of pain? It has been stated time and again that chlorpromazine augments or potentiates the depressant action of many drugs on the central nervous system. Our previous study[2] on experimental animals, utilizing the electroencephalograph, has demonstrated this effect especially with barbiturates. Such action has also been proved clinically. With the opiates and the opioids (demerol, dromoran, and nisentil), a similar effect can be shown although not as consistently as with the barbiturates. It has been proposed[3] that general anesthetics, nembutal and ether, act primarily by depressing the ascending reticular pathways. Since chlorpromazine potentiates the action of nembutal and also of ether, as observed clinically, it is not presumptuous to think that chlorpromazine may also act on the same area. It is also possible that chlorpromazine may intensify the analgesic action of the opiates and the opioids by interfering with the thalamic pain-integrating centers which are part of the ascending reticular pathways. The fact that patients do develop a detached attitude towards their pain leads one to suspect that some degree of euphoria or a like state is present.

Since chlorpromazine is a drug that is generally depressant to the central nervous system, it is highly tempting to conjecture that chlorpromazine augments analgesic action by contributing its depressant effects to the over-all action. This will not explain the previous finding that some bedridden patients became ambulatory. Can this salutory effect be reconciled with the depressant action? Severe pain seems to be somewhat relieved by bed rest and relief of this pain will encourage a suffering individual to get out of bed. Furthermore, as observed in experimental animals and in patients clinically, chlorpromazine depresses the central nervous system without actually causing marked degrees of somnolence.

Two other mechanisms may be proffered to explain the relief of pain, especially that involving the gastrointestinal tract. One of these is the depressant effect of chlorpromazine on the autonomic nervous system. Since pain arising from a hollow viscus is primarily due to distention, the depressant action of chlorpromazine may diminish this type of pain markedly. A corollary to this effect is the elimination of nausea and vomiting. The other mechanism, of course, is the calming and sedative effect chlorpromazine has on the patient. Anxiety always increases the intensity of any pain considerably. By decreasing this psychic factor, the tranquil state achieved probably contributes to the relief of pain. It must be pointed out that a few patients did not require narcotics after having received chlorpromazine.

CLINICAL APPLICATION

What seems to be outstanding is the difference in onset and degree of pharmacologic action shown by different routes of administration of chlorpromazine. Orally, the onset and intensity of effects are rather unpredictable. Larger doses have to be administered by this route than parenterally in order to produce the desired effect

though either route has its advantages and disadvantages. Intramuscularly, chlorpromazine may cause some degree of irritation. Fasciculations have been observed. However, it is a convenient, easy, and safe way of giving the drug. Intravenously, a little more technical skill is necessary. The onset of pharmacologic effects like somnolence, hypotension, and tachycardia are so rapid, depending on the dose, that great care must be taken to administer the drug slowly. Whenever the drug is to be given intravenously, it is desirable to dilute the ordinary 25 mg./cc. up to 25 mg. in 5 cc. Greater control over dosage may be achieved this way. The chief advantage of these parenteral routes is the consistently rapid development of effective pharmacologic action with relatively smaller dosages, particularly with the intravenous route. Administration of chlorpromazine with any narcotic should be almost in the manner of a biologic assay. Sufficient amounts of each drug should be determined by giving small increments of each concomittantly until the optimum dose needed to produce maximum relief is attained. 100 to 200 mg. of chlorpromazine in divided doses for a 24 hour period seems to give the best results.

As mentioned previously, hypotension is a side effect that might be undesirable. With the patient in the recumbent position, it is not a serious complication although occasionally severe drops in blood pressure have been observed, especially in the postoperative state. The tachycardia seen is sometimes alarming. It may be avoided or diminished by giving chlorpromazine in small doses until the desired amount is reached. Several of the patients in these studies complained of troublesome dreams and nightmares, some being erotic in nature. Such reactions had led a few of them to reject the drug.

CONCLUSIONS

From a statistical point of view, the series presented is probably not too significant. However, it remains interestingly impressive in that it is a fresh and useful approach to pain relief. Many additional patients have been observed since the pilot study and the results obtained parallel those initially observed, lending credence to the limited conclusions reached. Further studies employing a random blind controlled method are being carried out to find the actual place and value of chlorpromazine in dolorology.

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Experience with Chlorpromazine in Pediatrics

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The phenothiazine compounds introduced for clinical usage in the past few years have shown interesting and unexpected pharmacologic properties. One of the most interesting of these drugs is 10-(3-dimethylaminopropyl)-2-chlorphenothiazine hydrochloride, better known as chlorpromazine, and first synthesized in France by Rhône-Poulenc-Specia Laboratories. The purpose of this report is to sketch experiences of other workers and ourselves with this drug in pediatric application.

PHARMACOLOGIC PROPERTIES

The known multiple actions of chlorpromazine are enumerated in table I; the mechanism of action remains obscure in many instances.

The drug effects a neuroplegic action upon the autonomic nervous system at different levels, perhaps by chemical interference with the transmission of nervous impulses through the preganglionic, postganglionic, and peripheral synapses. There is more of a sympathicolytic than parasympathicolytic effect generally.

Chlorpromazine has diffuse effects upon the central nervous system including certain hypothalamic centers. These include hypnotic, sedative, and anticonvulsant effects. The control of body temperature and the basal metabolic activity may be influenced. Interesting too are its properties as a potent antiemetic and inhibitor of the conditioned reflexes. Less marked are certain other effects of chlorpromazine. Thus it has a mild activity as an antihistaminic and antispasmodic.

Experimentally, studies in mice suggest that it is possible to develop tolerance to the drug.[4] Some of our clinical observations lead us to suspect that this may also develop in children.

CLINICAL APPLICATIONS ABROAD

Following its synthesis and study in the laboratory, chlorpromazine was given diverse clinical trial in France and soon thereafter throughout the European continent. The reports of its effects were remarkably enthusiastic.

Chlorpromazine was first used in potentiated anesthesia by Laborit.[5] It was found very useful in the induction of artificial hibernation by Laborit and Huguenard[6] in the prophylaxis and treatment of surgical shock. Obstetricians found it helpful in the control of nausea and vomiting during pregnancy, and internists employed it for its antiemetic, anticonvulsant, and hypotensive effects in widely unrelated clinical conditions. Its effect on disturbed patients appealed to psychiatrists and its panacea-like properties aroused the ardor of clinicians balanced, however, by the keen eye of critical observers.

TABLE I

*Some Pharmacologic Properties of Chlorpromazine**

1. Neuroplegic
   - Sympathicolytic
   - Parasympathicolytic
2. Central depressor
   - Antiemetic
   - Hypothermic and antipyretic
   - Hypnotic
   - Depressor of conditioned reflexes
   - Anticonvulsant
   - Depressor of metabolism
3. Potentiator of other drugs
   - Analgesics
   - Sedatives
   - Hypnotics
   - Anesthetics
   - Curare-like substances
4. Antihistaminic (weak)
5. Antispasmodic (weak)

* See references (1, 2, 3) in bibliography.

In pediatric practice chlorpromazine was used in Europe chiefly to aid in the induction of artificial hibernations, in the care of premature infants and newborns with severe neonatal complications,[7] e.g., in the course of exchange-transfusions,[8] in cases of severe dehydration and shock,[9, 10] and assorted clinical conditions including respiratory disorders, meningo-encephalitis, and hypertensive encephalopathies.[10–12]

PERSONAL EXPERIENCES

In our hands chlorpromazine has been at times useful and at other times disappointing in its clinical effects. The latter is becoming less frequent as we familiarize ourselves with the conditions and dosages appropriate for given instances. Some of the pediatrics applications are listed in table II.

1. ***Antiemetic.*** We have previously reported[13] the results obtained with chlorpromazine as an antiemetic in pediatric practice. In approximately 75 per cent of patients we observed a satisfactory effect upon the vomiting associated with several unrelated conditions. That experience has continued with a much larger series of vomiting in infants and children.

2. ***Sedative.*** The exact mechanism of chlorpromazine as a sedative is obscure. Useful clinical results have been observed when chlorpromazine has been given with other known sedative drugs, e.g., barbiturates to potentiate their effects thus reducing the possibility of undesirable overdosage effects of the latter. Even when given alone chlorpromazine has been useful in reducing the involuntary hyperkinesia in cases of Sydenham's chorea and has potentiated the effect of barbiturates in the control of convulsions. Its antipruritic effect (perhaps due to its antihistaminic

action) was observed in such unrelated skin affections as varicella, dermatitis venenata, and erythema multiforme.

3. *Hypotensive.* As a blocking agent, chlorpromazine in adequate doses may cause a drop in blood pressure especially in the face of acute hypertension with or without acute hypertensive encephalopathy. Our observations have dealt with acute glomerulonephritis and the hypertension which may be observed in acute poliomyelitis.

4. *Aid for inducing hypothermia and artificial hibernation.* In 1938 one of us had the opportunity of participating, under the direction of Fay and Smith, in the care of many patients subjected to protracted hypothermia in the attempted but unsuccessful management of malignancy.[14] Observations made at that time implied numerous physiologic advantages which might have clinical application.

We have observed a reduction in the body requirements of oxygen, fluid, electrolytes, and calories, a marked tolerance for pain, and a reduction in pulse rate, activity of the heart, and prolongation of circulation time. Most recently Bigelow[15] and other investigators have applied these features for short term use in cardiac surgery. The ability to induce artificial hibernation successfully, safely, and swiftly was increased by the observations of Laborit and Huguenard[6] employing a "lytic cocktail"

TABLE II

Some Pediatric Applications of Chlorpromazine

I. Antiemetic effect
II. Sedative and tranquilizing effects
    Physical agitation, e.g., organic and other psychoses, chorea
    Pruritus
    Potentiation of analgesics
    Potentiation of barbiturates
III. Aid in induction of hypothermia and artificial hibernation with a view towards:
    1) Reduction of water and oxygen requirements, e.g., severe dehydration: diarrhea, hyperventilation (salicylism), etc.
    Shock: trauma, burns
    2) Reduction of oxygen and caloric requirements, e.g.,
        Cyanosis due to:
            a) Respiratory disorders, e.g., obstructive bronchiolitis, respiratory poliomyelitis, bronchopneumonia, etc.
            b) Central nervous system damage: brain injury, trauma, encephalitis, convulsions
        Pyrexia:
            Central: meningo-encephalitis, central nervous system injury, etc.
            Systemic: infections, disseminated lymphomas, and other neoplasms

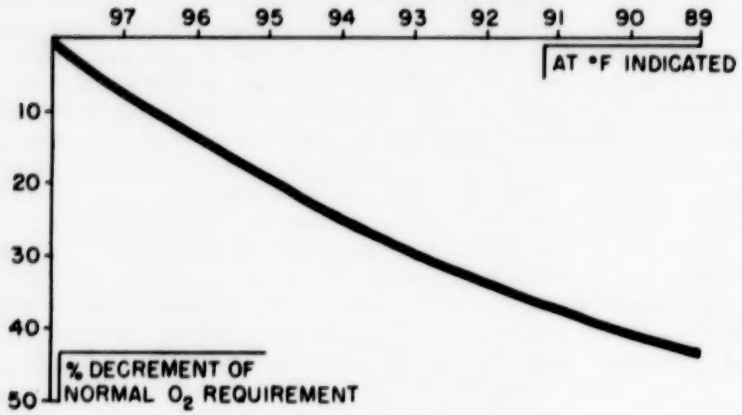
of chlorpromazine, promethazine, and meperidine. The influence of body temperature on oxygen requirement is strikingly illustrated in figure 1.

At cryotherapeutic temperature levels, not only is the total oxygen consumption reduced[16, 17] but a water economy is afforded, due to reduced urine flow and because of the reduction in the insensible water loss (through the lungs and skin). In clinical pediatrics this may be pure water loss, e.g., the hyperventilation induced by salicylism, or a combination of water and electrolytes, e.g., diarrhea and vomiting.

During periods of fever total oxygen requirements rise steeply. This may prejudice the successful outcome of severe illness in a hypoxic child. Control of such

Figure 1

INFLUENCE OF BODY TEMPERATURE ON OXYGEN REQUIREMENT *



* *Adopted from Bigelow (15) and Dundee (16)*

temperature rises by cool sponging is not always effective and requires constant application; "control" of fever by salicylates is unphysiologic, bringing about diaphoresis with loss of fluid and electrolyte.

DOSAGE AND METHOD OF ADMINISTRATION*

For antiemetic or sedative effects we employ approximately 4 to 5 mg./Kg. of chlorpromazine per day in four equally divided doses. Oral administration is preferred when feasible. The desired results are usually obtained within 12 hours following the administration of the first dose. The drug may also be given by deep intramuscular injection according to a similar dosage schedule. In children over 7 years of age we generally employ 25 mg. three or four times a day.[13]

For the induction of states of hypothermia or artificial hibernation we have been using the "lytic cocktail" of Laborit and Huguenard[6] in a simplified form. For this purpose we have observed that chlorpromazine orally does not have the prompt effect of parenteral administration. We employ an immediate dose of 1 mg./Kg. of chlorpromazine and 1 mg./Kg. of promethazine mixed in 50 to 75 cc. of 5 per cent glucose water or normal saline (depending on the initial status of the patient's electrolyte balance). This solution is administered by intravenous drip at a variable rate according to the size of the patient or the severity of his condition. On the

* Chlorpromazine is available as "Thorazine" in tablets of 10, 25, 50, and 100 mg.; as syrup—10 mg. per teaspoon, and in ampuls of 1 cc. and 2 cc. (25 mg./cc.). Abroad and in Canada, chlorpromazine is available as "Largactil."

average we give this initial amount in a period of 30 to 45 minutes. At the same time external cooling is applied (by means of freezer bags) to reduce the temperature to the desired level. The best clinical judgment has to be exercised for each individual since even in similar pathologic conditions the requirements may vary considerably. In some instances our aim has been merely to suppress the hyperpyrexia as such, and return the temperature to euthermic levels. In other circumstances our aim has been to reduce the temperature to subnormal limits. We do not ordinarily care to maintain prolonged periods below 90 F. It has been postulated[16] that the diminution of oxygen requirements for each degree of temperature below a certain point is insignificant while the risks inherent to excessive hypothermia become increased. Once the initial dose has been given we follow with the administration of a maintenance dose of chlorpromazine (5 mg. /Kg. /day) and promethazine (5 mg. /Kg. /day) added to the total amount of intravenous fluids calculated to be given for the 24 hour period. The maintenance dose may also be given by deep intramuscular injection in four equally divided doses. In hypothermic states the requirements of water and electrolytes are reduced; at a body temperature of 90 F., we employ approximately 50 per cent of the basal requirements. We find it helpful to examine the serum for chloride level periodically.

When shivering occurs during induction of hypothermia we proceed with the immediate intravenous administration of sodium amytal (60 to 120 mg. is generally effective). Occasionally, in cases with extreme initial agitation we have used meperidine in doses of 2 mg. /Kg. added to the other components of the "lytic cocktail." The recommended doses of chlorpromazine and promethazine may need to be adjusted during the period of hibernation if it proves difficult to maintain the particular hypothermic level desired. Liberal external application of cold (freezer bags) is needed during the initial stage primarily.

For children over 7 years we give an immediate dose of 25 mg. of chlorpromazine and 25 mg. of promethazine. The maintenance dose is estimated at 100 mg. of each drug per day, using individual judgment.

The duration of the hibernation period depends on the process under management and on the individual's tolerance. A period of stabilized hypothermia of 72 to 96 hours has served our purpose in a number of instances. To re-establish normal temperature the drugs are discontinued and external heat is gradually applied. A transitory mild hyperthermia is not infrequent at this stage but is not generally significant.

It is beyond the purpose of this report to discuss hibernation therapy in pediatrics as such, but we believe it provides numerous clinical-physiologic advantages and can now be more effectively applied because of chlorpromazine. Two illustrative cases will serve to exemplify the principles established above:

Case No. 1. A 4 year old boy, was readmitted for a second relapse of acute leukemia. His leukemia was now resistant to chemotherapy and the clinical course was progressively downhill, accompanied by a septic type of fever with no evidence of infection and unresponsive to antibiotics and antipyretics. The application of freezer bags was ineffective and not tolerated because of extreme discomfort. On the eighteenth day, intravenous administration of chlorpromazine and promethazine was

started and the temperature dropped from 103 to 99.8 degrees in the short period of two and a half hours. With continuous administration of intravenous fluids containing the above-mentioned blocking agents the patient remained afebrile and comfortable. He received this medication for four and a half days and subsequently remained afebrile until death from internal hemorrhage occurred on the twenty-fourth day.

Case No. 2. A 2½ year old white boy, was admitted with severe bulbospinal poliomyelitis which necessitated tracheotomy and care in a tank respirator. Extraordinarily high displacement pressures (32 to 40 cm. of water) at cycle rates of 28 to 30 per minute were required. Attempts at gradual weaning were greatly complicated by three distinct episodes of bronchopneumonia, by vomiting (which yielded to chlorpromazine), and the continued necessity for extreme ventilatory displacement which included supplementary positive pressure delivered by anesthesia bag via the tracheotomy.*

In the thirteenth week another severe episode of bronchopneumonia appeared. The child was febrile, cyanotic, and comatose despite maximum tank-respirator pressures and rate combined with anesthesia bag delivery of oxygen via the tracheotomy. In an effort to reduce respiratory requirements, artificial hibernation was induced by chlorpromazine and promethazine administered intravenously with external application of freezer bags. An average body temperature of 90 F. was maintained for six days, with marked improvement in ventilatory status. The neuroplegic blocking agents and external cold were discontinued with a return to normal body temperature color and state of consciousness. Weaning from the respirator was at last possible.

SIDE EFFECTS OF CHLORPROMAZINE

The most frequently observed side effect of chlorpromazine has been mild drowsiness which is not disadvantageous in the types of children we have treated. This is reversible when the medication is discontinued.

Abdominal and bladder distention were less common but worthy of note. They are generally not severe and subside easily under parenteral administration of prostigmin. Several investigators have reported transient obstructive jaundice in patients treated with chlorpromazine.[3, 18, 19] In our series jaundice has been observed in only three children, in each of whom there was pre-existing severe liver damage in the course of lymphoma with sepsis.

DISCUSSION AND SUMMARY

The synthesis of chlorpromazine has resulted in a potent addition to the therapeutic armamentarium of the pediatrician who must often treat along symptomatic lines dictated by physiologic considerations. A review of table I which indicates some of the known pharmacologic effects brings out the possibilities of clinical applications such as those observed in table II.

* The heroic efforts of the house staff in maintaining prolonged ventilation during several periods of organic death were well-rewarded by the results.

We are especially interested in further developing the application of systemic hypothermia to a variety of otherwise severe and mortal conditions. The stabilizing effect of chlorpromazine makes such therapy more reliable and feasible, and thereby offers the clinician a means for economy of oxygen, water, electrolyte, and calories in desperately ill children.

ACKNOWLEDGMENT

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Epilogue

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Since its introduction in Europe in 1951 and in this country in 1953, chlorpromazine has been the subject of approximately 400 articles dealing with its clinical utility in almost all fields of medicine. The preceding papers admirably cover the present major uses of the drug and cogently lead one to speculate about uses yet to be uncovered. But chlorpromazine is more than a versatile therapeutic tool. Because of its diverse pharmacologic activity, it is a guidepost from which to direct further study of basic physiologic and psychologic functions.

A review of its various activities reveals widespread effect on the central nervous system, particularly on the autonomic centers. For example, the abstinence syndrome produced by abruptly withdrawing narcotics from addicts is completely abolished with chlorpromazine therapy. A few of its other effects include depression of the emetic chemoreceptor trigger zone, inhibition and often reversal of the pressor effect of epinephrine, and control of anxiety and conditions simulating hypothalamic rage.

Taken as a whole, the sum effect of chlorpromazine may be considered as an altering of body reaction to noxious stimuli and resultant stress, either from the external or internal environment. This is somewhat analogous to the effects of ACTH and cortisone on various tissue systems to alleviate disastrous over-reaction to stress. Use of chlorpromazine in the field of psychiatry is particularly rewarding, since in mental disorders the reaction to stress is frequently so great that the patient loses all contact with those who are trying to help him. Controlling the reaction with electroshock and insulin shock therapy and with surgical lobotomy usually hampers physician-patient rapport, whereas chlorpromazine, while alleviating the reaction, actually facilitates the interpersonal relations so necessary for baring and treating the underlying emotional conflicts.

The fact that chlorpromazine antagonizes epinephrine and its derivatives, which in large doses produce a quasi-psychotic effect characterized by anxiety, furnishes a clue to the understanding and combating of anxiety states. Moreover, the dampening effect of chlorpromazine on experimentally induced psychoses brought on with lysergic acid derivatives and mescaline may, with further study, hopefully provide a lead to the etiology of mental disorders on a biochemical basis.

With chlorpromazine and other new agents, notably Rauwolfia alkaloids, lysergic acid derivatives, mescaline, and epinephrine derivatives, we stand on the threshold of momentous discoveries in the field of the reaction of the body to stress. Just as the problems of infectious diseases have been hurdled to an undreamed of degree in recent years, we appear to be on the brink of surmounting the major obstacles in the treatment of nervous and emotional disorders.

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FOREWORD

The objective of the QUARTERLY REVIEW OF OTORHINOLARYNGOLOGY AND BRONCHOESOPHAGOLOGY, now incorporated in the INTERNATIONAL RECORD OF MEDICINE, is to bring together in one publication, in concise form, the essence of all that is published in otology, rhinology, laryngology, bronchology and esophagology from the world's voluminous literature, so that with a minimum of time and expense you are enabled to keep abreast of the rapid progress in these special fields of medicine and surgery.

The organization and simplification of the new data and the separation of the less significant findings from the important facts keep you continuously posted. The QUARTERLY REVIEW OF OTORHINOLARYNGOLOGY AND BRONCHOESOPHAGOLOGY brings you many new clinical discoveries—improved technics—world-wide research—a vast fund of important data, all in concise form.

The clinical facts presented here are systematically gathered from every available source. They are condensed from more than 300 medical and surgical periodicals, transactions and special publications and are properly classified and indexed for quick reference.

A section entitled "The International Record of Otorhinolaryngology and Bronchoesophagology" is included and consists of advanced experimental and clinical reports in otorhinolaryngology and bronchoesophagology.

Quarterly Review of **OTORHINOLARYNGOLOGY AND BRONCHOESOPHAGOLOGY**

Incorporating the International Record of Otorhinolaryngology and Bronchoesophagology

ABSTRACTS

pharynx

1. *Nasopharyngeal Fibroma: A Clinico-Pathological Study of Seventy Cases.* PROFESSOR HANDOUSA, HOSNY FARID, AND ANWAR M. ELWI, Cairo, Egypt. J. Laryng. & Otol. *68*:647–666, October 1954.

The authors report on 70 authentic cases of nasopharyngeal fibroma which they have examined and treated in the last 20 years. About an equal number was dropped because the histologic blocks and slides could not be traced for restudy.

The authors are of the opinion that the lesion is a true tumor and not an allergic condition or inflammatory in nature. The tumor is so vascular in 66 cases as to justify the term angiofibroma. There is no true capsule for the tumor. Vascular channels lined with one layer of endothelium are seen in every case. Arterial channels with a thick muscular coat are seen in 28 cases and in 9 of these, some of the arteries show a defect in the muscular coating. Thrombosis may occur in either type of vessel. Necrosis of parts of the tumor due to ischemia resulting from thrombosis seems to explain the diminution in size of nasopharyngeal fibroma noted by some observers, and provides good evidence against the theory of uniform regression at sexual maturity.

Among this series, 51 were males and 11 were females. The age varied from 8 and 50 years. This proves that the disease is neither exclusive to males nor to the age of puberty.

The growth is usually attached to one side of the nasopharynx above the level of the nasopharyngeal opening of the Eustachian tube in relation to the part of the nasopharyngeal wall which is normally free from muscle fibers. It was never seen attached in front of the upper two cervic vertebrae and the findings favor periosteal origin of the tumor.

The routes of extension of the tumor were discussed. Extension to cheek was met with in 9 cases. It was proved radiologically that the growth winds round the outer border of the maxilla after passing outwards through the pterygomaxillary fossa to reach the infratemporal region. It never extended through the maxillary antrum to perforate the anterior or outer wall to reach the cheek.

Signs and symptoms were discussed. Two cases of rhinoscleroma developed masses which attained a large size and hung down in the nasopharynx simulating nasopharyngeal fibroma, consequently rhinoscleroma should be taken into consideration in differential diagnosis. The authors are of the opinion that radical surgical excision is the ideal method of cure in cases fit for operation. For the line of approach, they prefer the use of a combination of the oral route and an external approach (Moure's lateral rhinotomy) as the latter provides a shorter and more direct route to the base of the tumor than does Denker's. The attachment of the tumor is bimanually located; the mucosa is cut through next to it by a suitable curved periosteum elevator. Dissection is carried out by gauze which is forced in between the base of the tumor and the underlying bone by the periosteum elevator. This is repeatedly done using both routes alternately; while one route is being used, the wound of the other is kept tightly packed with gauze. As the growth is set free, it is removed by the oral route and the bed is quickly packed by a long strip of vaseline gauze.

The authors do not use the transpalatal route in order to avoid repairing the soft palate which would take more time and may be unsatisfactory. The operation is performed under general anesthesia, preceded by tracheotomy, and packing of the pharynx. During the operation, blood transfusion is given routinely by the drip method to compensate for any loss of blood during dissection of the tumor. 6 references. 14 figures.—*Author's abstract.*

otology

2. *Observations on the Circulation in the Cochlea.* J. C. SEYMOUR, London, England. J. Laryng. & Otol. *68*:689–711, October 1954.

In order to study the behavior of the cochlear vessels to vaso-active stimuli, a technique was developed to expose the capillary fields of the spiral ligament and at the same time maintain physiologic conditions. From these observations it has been adduced that the activity of the arterioles, metarterioles, and precapillary sphincters of the cochlear vessels in response to 1/10,000 adrenaline solution and histamine is not "paradoxic" as has hitherto been reported from indirect methods.

The independence of the circulation in the stria vascularis from that in the spiral ligament has been confirmed, and also the continuity from apex to base of the cochlea. The speed of circulation in this network of capillaries appears to be slower than in that of the spiral ligament to enable maximum metabolic exchanges to occur between the endolymph and blood.

The production of endolymph in the scala media does not normally occur in the absence of vascularization of the stria vascularis as seen in congenitally deaf animals, deaf mutes, and in rubella studies.

Although it is believed there is a slow endolymph current towards the saccus endolymphaticus and that absorption occurs in it, histologic examination of the walls indicates quite the contrary point of view. There appear to be at least four

types of secretion contributing to the endolymph in the saccus. Two types are provided from specialized papillae; some have a capillary network in their cores, others have nonvascular cores. From these papillae, as at other sites, cells may be seen to liberate their contents into the endolymph or to float off into the lumen of the saccus where they break up. The third variety of secretion is formed by the extrusion of globules at the free border of the living cells. The fourth contribution may be produced from the rich capillary network around the saccus but especially at its distal end. The peculiar composition of the endolymph supports this view, especially the fact that its potassium content is 20 to 30 times that of perilymph, suggesting that it is formed largely of the cytoplasm from living cells.

These views are not in agreement with the belief that the saccus absorbs endolymph but they do explain histologic findings and other observations such as the presence of endolymph in the saccus in deaf mutism. The utriculo-endolymphatic valve prevents reflux of endolymph from the utricle and since the stria and saccular macula are not developed in these cases, there is no endolymph secretion in the scala media and sacculus. Hence, the presence of endolymph in the saccus suggests that secretion takes place in it.

In the light of these findings, which are at variance with present concepts, a number of considerations are offered in explanation of some otologic disorders, the most important of which is a reconsideration of the "vascular factor." 28 references. 18 figures.—*Author's abstract.*

3. *Hydrocortisone Acetate and Neomycin in Otic Infections.* BEN B. SENTURIA AND VERNA ALFORD, St. Louis, Mo. Laryngoscope. *64*:834–844, October 1954.

A study of the literature showed that excellent results had been obtained from the use of hydrocortisone acetate and neomycin in various dermatoses. Therefore, an aqueous suspension and/or an ointment containing neomycin (5 mg.) and hydrocortisone acetate (15 mg. per c.c. or gram) was used in a series of 90 patients (114 ears) with various otic infections.

With the exception of otomycotic lesions, which failed to improve until the fungi were identified and eradicated, excellent results occurred in the neurogenic type of external otitis and recalcitrant infections of post-fenestration and post-mastoidectomy cavities. Patients with chronic otitis media, acute and chronic diffuse external otitis, showed beneficial results.

In general this study points up the increasing necessity for the otologist and dermatologist to note clearly the differential diagnosis of diseases of the external ear. Only by appreciating the morphologic differences and the bacterial flora usually present in these various categories of diseases of the external ear can prompt and proper therapy be applied. 19 references. 2 tables.—*Author's abstract.*

4. *The "Pediatric Ear" and Antibiotics.* ROBERT HENNER, Chicago, Ill. Eye, Ear, Nose & Throat Monthly. *33*:530–532, September 1954.

This article deals with the evaluation of the results that can be achieved with proper and complete antibiotic care, and the dangers of inadequate care. It

stresses the indications for paracentesis, mastoidectomy, and other forms of surgical intervention in light of our present knowledge. Principles of preservation of the function of hearing and prevention of masked complications are the keynote of modern day therapy.—*Author's abstract.*

laryngology

5. *Stripping of the Vocal Cords.* S. MUKERJI, Minot, N. Dak. J. Laryng. & Otol. *68*:726–729, November 1954.

Stripping of the vocal cords has been a procedure long practiced for essentially hypertrophic lesion of the vocal cords, though it is not very popular today. Interest in this method seems to have arisen from studying the histopathologic structure of vocal cords in patients after laryngo-fissure operations and from observations on cats, chiefly by Loré.

Passing mention is made in the article concerning the etiologic aspect of hypertrophic conditions of the larynx. In all such cases a misuse or over-use of the voice is almost always encountered. Constant trauma to the cords with resultant localized inflammation is supposed to be the basis of hypertrophic changes. The author discusses the technique of stripping of cords and believes a general anesthesia is more helpful in achieving satisfactory results, though he has used local anesthesia in both the cases reported by him. The use of the Imperatori subglottic forceps is also suggested.

Exposure of the anterior commissure is essential, especially when complete stripping of the cords is planned. In all cases, the lesion is grasped and traction exerted along the longitudinal axis of the cord without cutting too deeply into the mucous membrane.

The author discusses the pros and cons of whether to strip both cords at the same sitting. The consensus is to strip one cord at a time with a few days interval to prevent subsequent web formation. Two case histories are reported. 3 references.—*Author's abstract.*

bronchology

6. *Endoscopic Observation in Various Types of Bronchial Obstruction: A Study of 50 Cases.* HERBERT H. HARRIS, Houston, Tex. Texas State J. Med. *50*:665–668, September 1954.

Bronchial obstruction is clinically manifested in two ways—by obstructive emphysema and obstructive atelectasis. Emphysema is usually the first finding of bronchial obstruction though sometimes not recognized as such. Atelectasis usually follows this partial obstruction when either the bronchus has been completely obstructed by the disease or the cohesiveness and adhesiveness of the secretions have completed the obstruction.

A review of the physiology of the upper respiratory tract which indicates the importance of the ciliated columnar epithelium lining the tract is included. The forces which tend to drive out foreign substances, such as ciliary wafting tussive squeeze, and the bechic blast are stressed. These may be impaired by over sedation, by paralysis, and generalized weakness due to debility.

A series of 50 selected cases were analyzed to determine whether there were any new conceptions. In the study of 19 cases of foreign body the conclusions are that early obstruction almost always causes emphysema. Some of the patients showed no evidence of an atelectasis even after four or five days.

Bronchogenic carcinoma causes emphysema early, though it is not often recognized. This can sometimes be seen at bronchoscopy. Mediastinal tumors more frequently cause obstructive emphysema than atelectasis.

Tuberculosis in the child is often of the primary type, caused by pressure or erosion from the mediastinal nodes, while that of the adult is from alveolar disease with secondary extension and obstruction of the bronchi. No unusual information regarding postoperative atelectasis was observed in the cases presented. Several cases of inflammatory obstruction were seen but nothing particularly new was recognized by the bronchoscopic study.

The usual signs of the crescent-shaped bronchus were recognized in the patients who had asthma, but in those who were in a period of remission this finding was not noted. In poliomyelitis for patients who are in a respirator and have had a tracheotomy, a bronchoscopy is suggested if respiratory difficulty is encountered, because of the secretion frequently retained in the left main stem bronchus. These are sometimes not removed by tracheal aspiration through a tracheotomy tube because the catheter more frequently enters the right main bronchus than the left. 10 references. 1 table.—*Author's abstract.*

7. *Pathologic Changes of the Skin of the External Auditory Canal in Chronic Otitis Media and Mastoiditis.* L. H. SOPHIAN, Z. K. COOPER, AND BEN H. SENTURIA, St. Louis, Mo. Ann. Otol., Rhin., & Laryng. *63*:261–265, June 1954.

Portions of the external auditory meatal skin were obtained during mastoidectomies from 40 cases of chronic otitis and mastoiditis. Serial sections were prepared and examined microscopically. In all cases examined, notable degrees of involvement of the external ear by a chronic inflammatory process were demonstrated. Pathologic findings included edema, cellular infiltration, vascular hyperplasia, vascular obliteration, necrosis in the supporting tissue, focal degeneration of the apocrine glands, and epidermal thickening with hyperkeratosis frequently resulting in obstruction of the orifices of ducts.

The distribution of the inflammatory and degenerative lesions appears to be characteristic in this type of chronic otitis externa. The greatest involvement is found in the deepest layers of the dermis, rather than in the superficial layer. The epidermal changes appear to be secondary rather than primary. While obstruction of ducts is often found, the mechanic factor does not appear significant as there is no evidence of accumulation of secretion.

The authors conclude that one of the basic alterations in chronic otitis externa associated with chronic otitis media and otorrhea is inflammatory degeneration of the apocrine glands. The authors go on to express the opinion that their evidence supports the theory that extension of the inflammatory process to the skin of the external ear canal is lymphogenous or hematogenous, rather than through the epidermis by direct penetration of pathogens from surface exudate. 12 figures. 1 table.—*Author's abstract.*

8. *The Inarticulate Child: A Problem in Diagnosis.* J. W. MC LAURIN, Baton Rouge, La. Laryngoscope. *64*:454–466, June 1954.

Although the inarticulate child is being referred to the otologist more frequently than ever before, there is still a tendency to delay investigation of his difficulties for too long a time. It is never too early to start testing and training him, and also never too late, though the end results are less effective when treatment is put off.

The belief persists in many quarters that the inarticulate child must be investigated by elaborate laboratory methods. Actually, pure tone audiometry, psychogalvanic skin-resistance audiometry (PGSH), electro-encephalography, and pure tone audiometry by peep-show methods are not suitable for the diagnosis of speech and hearing defects in young children. Instead, diagnosis is accomplished, and in this order, by detailed history-taking and clinical observation and evaluation, with laboratory investigation last of all. The use of noise-makers in a free field, by the so-called cessation of activity technique, is a desirable method of testing hearing in young children because it can be done unobtrusively and in natural circumstances. These simple clinical methods are highly effective but they take time, and observation must be careful and thorough.

The differential diagnosis can be arrived at by the evaluation of response to sound, visual clues, speech, use of gestures, laughing, smiling and crying; other senses, motor behavior, the child's attention to the facial expressions of others, his emotional expression and development; his social perceptions, perseveration, distractibility, and disinhibition. When these are properly studied and evaluated, the differential diagnosis between impairment of hearing, emotional disturbance, mental deficiency, and aphasia is usually possible.

The approach to the problem should be entirely scientific, but the physician must not forget that both the child and his parents are human beings in distress, who need all of the understanding and compassion of which he is capable in addition to his technical skill. 6 references.—*Author's abstract.*

9. *Tumori Metastatici Dell'Osso Temporale.* H. BRUNNER, Newark, N. J. Archivio Italiano Otologia Rinologia e Laringologia. *64*:800–817, November-December 1953.

The microscopic findings in a case of metastatic tumor in the temporal bone are presented. The finding of displaced portions of the parotid gland in the wall of the jugular bulb is also reported. There are two findings that are noteworthy:

(a) The tumor forms a large nodule in the floor of the tympanic cavity. The nodule displaces and invades the aberrant portion of the parotid gland and extends upward to the drum. It is likely that the tumor would have grown through the drum into the external auditory canal if the patient had lived long enough.

(b) The tumor invades the skin of the external canal and may cause, in the presence of an intact drum, a sagging of the superior and posterior wall of the external canal similar to the finding in infections of the mastoid antrum. 4 references. 12 figures.—*Author's abstract.*

10. *Valore Dell'Esame Audiometrico Vocale Nella Valutazione Dei Risultati Pratici Del Cosidetto "Metodo Misto."* GIAN BATTISTA LEONARDELLI, Milan, Italy. Archivio Italiano Otologia Rinologia e Laringologia. *64*:842–854, November-December 1953.

An investigation is made by the author on the value of audiometric examination in order to appreciate the practical results of the "mixed method," inaugurated two years ago as a complementary system to teach normal labial reading to the pupils of the Milan School for Deaf-mutes, presenting an auditive loss so as to allow a proper application of the aforesaid method.

The researches, carried out on 21 pupils, involved a tonal acoustic functional examination (constantly completed by a recruitment research) followed by a vocal audiometric examination performed according to the following modalities:

(a) Vocal audiometric examination with an amplification varying from 75 db. above the normal perception threshold to 0 db. and simultaneous labial reading.

(b) Vocal audiometric examination without any labial reading.

All audiometric researches have been performed in the silent room by the same investigator. Properly chosen sounds or articulations, taken from Bocca's and Pellegrini's lists, have been used for each pupil, according to the class attended.

A few practical conclusions are drawn from the above inquiry and summarized as follows:

(1) The labial reading capacity allows, even if it is very moderate, the conversation for amplification values considerably lower than those requested by the single use of residual auditive power.

(2) A following amelioration of labial reading capacity parallelly determines the use of lower amplification values.

(3) When labial reading or amplification appears insufficient in itself, the association of these two means allows an excellent comprehension of conversation.

(4) Such an advantage is less and less evident, and progressively becomes ineffective with the progressive annulment of the efficiency of one mean or the other (chiefly of the acoustic one). 10 references. 5 figures. 1 table.—*Author's abstract.*

11. *Capillary Areas of the Membranous Labyrinth.* CATHERINE A. SMITH, St. Louis, Mo. Ann. Otol., Rhin. & Laryng. *63*:435–447, June 1954.

These studies represent a comparative analysis of the capillary areas in the cochleas of the guinea pig, the cat, and the human. The blood vessels of human ears

were studied by means of the benzidine stain. Those of the cat were made visible by intravascular precipitation methods.

The vascular pattern of the capillary areas in the spiral ligament shows some variations. A single vessel coursing in a spiral direction is found in the spiral prominence of the guinea pig; a narrow rolled network of vessels can be seen in this area in the cat and the human. There are only a few superficial vessels in the upper and lower spiral ligament of the guinea pig and the cat although these areas show extensive networks in the human. The major difference seen in the spiral lamina was the absence of the vessel beneath the tunnel in most of the cats.

Although these general differences have been observed, the distribution of small blood vessels in the spiral ligament and spiral lamina of the cochlea of the three species is very similar. The variations seem to be secondary in character when compared to specie variations in structure. 10 references. 9 figures.—*Author's abstract.*

12. *Ventriculomastoidotomy: Its Significance to the Otologist.* GEORGE F. REED, Boston, Mass. Ann. Otol., Rhin. & Laryng. *63*:273–277, June 1954.

Mastoidotomy is a fairly new operation for the relief of internal hydrocephalus. It is a shunt-type procedure in which the lateral ventricle of the brain is connected with the mastoid antrum.

The surgical procedure and the management of the case is primarily a neurosurgical endeavor though the otologist can be of great assistance to the neurosurgeon, at the time of operation, in the preoperative evaluation of the patient, and in the postoperative care of the patient. The article describes the operation in some detail with special reference to the otologist's role at the time of operation.

Three cases, done in conjunction with the neurosurgical service of the Massachusetts General Hospital, are cited briefly. 4 references.—*Author's abstract.*

13. *Irrigation of Nasopharynx after Adenoidectomy.* D. A. DE LISA, New York. Laryngoscope. *64*:795, September 1954.

A simple technique of irrigation of the nasopharynx with cold saline at the conclusion of the operation is described. The gauze packing is removed from the nasopharynx and cold normal saline at about 60 F. is flushed slowly into each nostril with a rubber bulb syringe and simultaneously removed from the pharynx with the aspirator. The procedure is repeated until all oozing has stopped. The cold water constricts vessels and washes out clots. The author's previous incidence of about 3 per cent postadenoidectomy bleeding was reduced to none in 193 cases with the irrigation technique.—*Author's abstract*

14. *Deafness Due to Rubella.* H. O. LANCASTER, Sydney, Australia. M. J. Australia. *2*:323–324, August 28, 1954.

Geographic isolation is considered as a factor in the epidemiology of rubella and measles. The short epidemic waves of measles in England are compared with the

longer and more irregular waves in Australia. The same comparison could be made if data was available for rubella. Isolated countries such as Australia and New Zealand have had epidemics of births of the deaf, but in countries that are part of large populous land masses, such as England, Sweden, and Italy, epidemics of rubella are probably frequent with females tending to acquire the disease and consequently immunity in childhood. (A full discussion is to appear in *Acta Genetica et Statistica Medica*, vol. 5.) 7 references.—*Author's abstract.*

15. *Use of Refrigerated Homogenous Bone Graft for Microgenia in the Maxillofacial Triad.* IRVIN J. FINE, Perth Amboy, N. J. Eye, Ear, Nose & Throat Monthly. *33*:591–593, October 1954.

The maxillofacial triad is a term suggested by Goldman to designate a characteristic facial deformity caused by nasal obstruction as a result of trauma in early childhood. The correction of the specific nasal deformities by the new Goldman technique and of mandibular retrusion by implanting refrigerated bone between the mandible and the soft tissue is also described.

Clinically, autogenous cancellous bone grafts have proved most successful. On roentgenographic examination, the new bone formed on the chin appears to be indistinguishable from that of an autogenous cancellous bone graft. The concept that bone grafts act as a scaffold and stimulate osteogenesis is clinically confirmed. 1 reference. 3 figures.—*Author's abstract.*

16. *Psychogenic Deafness.* P. F. KING, London, England. J. Laryng. & Otol. *68*: 623–635, September 1954.

Psychogenic deafness is a convenient term which conveys no clear-cut picture of any aural disorder. It may be classified as follows:

1. *Functional deafness*
   (1) Loss of discriminative faculty (Kopetzky),
   (b) Organic deafness with hysteric overlay,
   (c) Pure hysteric deafness with no evidence of organic defect.
2. *Malingering*
   (a) Malingering associated with hysteria,
   (b) Malingering with organic defect,
   (c) Simple malingering.

Loss of the Capacity for Discriminative Listening—This occurs in patients in the older age groups, in deaf children, and in deaf adults who have not been rehabilitated by an aid or lip reading. I have seen 9 cases in young male adults employed on responsible "listening" jobs in telecommunication, in all the hearing was normal.

Functional Deafness—Chubb (1946) gives the following definition, "Cases of hysterical deafness have on the one hand no organic lesion to account for the deafness, and on the other no conscious responsibility for the deafness present. They have nothing in common with the deliberate malingerer except the absence of an organic lesion." The incidence of the condition is unknown and the frequency with which it occurs under combat conditions varies from one writer to another.

Hysteric deafness may occur alone or be associated with organic deafness. A total of 12 cases of the latter nature were seen. In addition to 19 cases of pure functional deafness, there was a history of some form of aural disease in 12. Both types occur in those of low mentality, poor education, and ebbing morale.

The Detection of Functional Deafness—This may be difficult if an organic deafness has a hysteric overlay. Unilateral deafness is more common than bilateral deafness, except in cases of organic deafness with hysteric overlay.

A history of sudden onset of hearing loss should be suspect. The demeanor of the patient may help though responses to whisper and tuning fork tests may show divergent results. The patient with hysteric deafness reacts as though his hearing loss is real, and because of this ordinary tests for proving malingering are not very helpful.

The Use of Audiometric Tests—Doerfler and Stewart (1946) found that a consistency of response on successive audiometric tests was not always necessarily indicative of organic deafness. They discovered this consistency in patients with functional deafness and assumed that the patient employs a figurative yard stick against which all sounds are gauged.

We employ ascending and descending scales of intensity in testing with pure tone audiometry and these generally show divergent findings on the first test.

The "efficiency" test in which the subject listens to recorded speech at an intensity of 106 decibels in a background noise of 100 decibels has been used. The scores obtained are far below those of patients with the most advanced form of perceptive loss. This corresponds with the finding of Doerfler and Stewart, that when noise is introduced in measured quantity into a system where speech is already present that the patient with psychogenic deafness responds in a different manner from the patient with normal hearing or one with organic loss.

Psychogalvanic tests have been used by other writers.

The Value of Tests of Labyrinthine Function—The value of these tests is debatable since a normal response is not necessarily evidence of hysteric deafness.

Management—Early diagnosis is imperative and though suggestions may be given by the otologist, later care should be by the psychiatrist. The use of the pentothal abreaction is advocated. During the abreaction the psychiatrist may get an insight into what has precipitated the deafness. Suggestions can be attempted in the period of recovery. Three typical cases are described.

Malingering—This occurs as an entity, but is also associated with organic deafness and sometimes with hysteria. Generally, unilateral deafness will be simulated as the pretense is easier to maintain. There may be an associated self-induced otitis externa. Lombard's test and repeated audiometry are favored in detecting the malingerer. 13 references. 5 figures.—*Author's abstract.*

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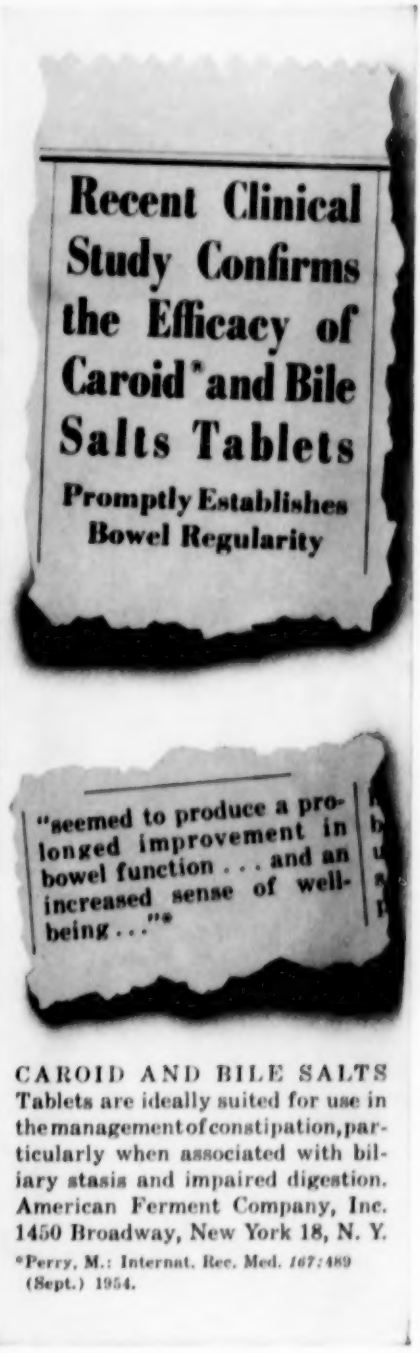
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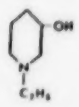

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